ISSN 0004-2803
ISSN 1678-4219 on-line
Coden ARQGA

ARQUIVOS DE GASTROENTEROLOGIA

Número 2 | Abril/Junho 2020 | Volume 57

ARCHIVES OF GASTROENTEROLOGY

Publication of the Brazilian Institute for Studies and Research in Gastroenterology and others Specialities - IBEPEGE

Founded in 1963 by Prof. Dr. José Fernandes Pontes

IBEPEGE
Instituto Brasileiro de Estudos e Pesquisas de Gastroenterologia e Outras Especialidades

ORGÃO DE DIVULGAÇÃO
Publication

CBCD
Colégio Brasileiro de Cirurgia Digestiva

FBG
Federação Brasileira de Gastroenterologia

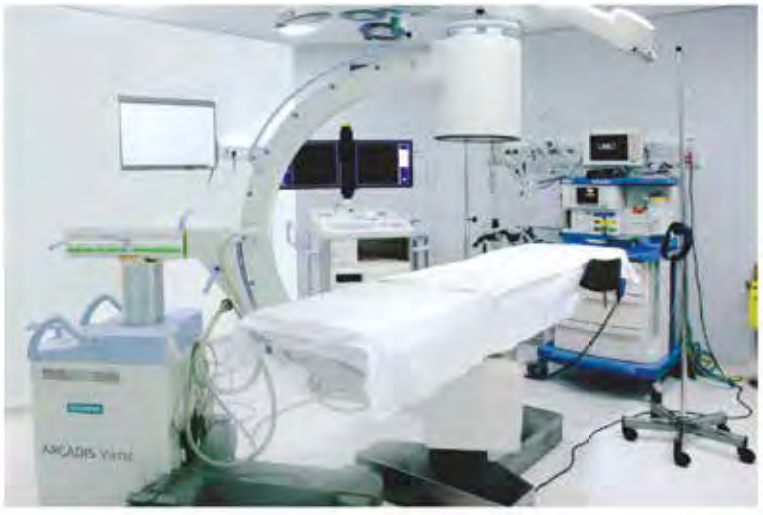
SOBED
Sociedade Brasileira de Endoscopia Digestiva

SBNPE
Sociedade Brasileira de Nutrição Parenteral e Enteral

SBMDN
Sociedade Brasileira de Motilidade Digestiva e Neurogastroenterologia

SBH
Sociedade Brasileira de Hepatologia

ABD
Academia Brasileira de Disfagia



O IGESP, um hospital geral com perfil cirúrgico que é referência no atendimento de alta complexidade, agora também vai ser referência em modernidade.

Além de especialistas renomados e do seu centro cirúrgico de última geração, o IGESP agora também conta com novas instalações e serviços, garantindo maior segurança aos médicos e maior conforto para pacientes.

HOSPITAL IGESP

O melhor pra você

R. Silvia 276 | Bela Vista
São Paulo | SP | 11 3147.6200
www.hospitaligesp.com.br

MKTONE

UMA ESTRUTURA MODERNA QUE REFLETE A NOSSA VOCAÇÃO: O CUIDADO COM A VIDA.

Uma empresa do grupo

Trasmontano
Saúde

ARQUIVOS DE GASTROENTEROLOGIA

ARCHIVES OF GASTROENTEROLOGY

IS THE OFFICIAL PUBLICATION OF:

Brazilian Institute for Studies and Research in Gastroenterology and Other Specialities (IBEPEGE)
Alcides Felix Terrivel (Representative)
Brazilian College of Digestive Surgery (CBCD)
Delta Madureira Filho (President)
Brazilian Federation of Gastroenterology (FBG)
Schlioma Zaterka (President)
Brazilian Society of Digestive Endoscopy (SOBED)
Jairo Silva Alves (President)
Brazilian Society of Parenteral and Enteral Nutrition (SBNPE)
Melina Gouveia Castro (President)
Brazilian Digestive Motility & Neurogastroenterology Society (SBMDN)
Ricardo Guilherme Viebig (President)
Brazilian Society of Hepatology (SBH)
Carlos Eduardo Brandão (President)
Brazilian Dysphagia Association (ABD)
Ana Furkim (President)

Expediente / Editorial Office
Mariana Rodovalho

Redação e Administração / Correspondence
Rua Dr. Seng, 320 – Bela Vista – CEP 01331-020 – São Paulo, SP – Brasil – Tel.: (11) 3147-6227
E-mail: secretariaarqgastr@hospitaligesp.com.br

Quarterly publication. The journal ARCHIVES OF GASTROENTEROLOGY is abstracted and/or indexed in: EMBASE / Excerpta Medica, Hygiene and Communicable Diseases (CAB Abstracts), LILACS, PUBMED / MEDLINE, Periódica (Índice de Revistas Latinoamericanas en Ciencias), Tropical Diseases Bulletin (CAB Abstracts). Online: http://www.scielo.br/ag

ISSN 0004-2803
ISSN 1678-4219 - on-line
Coden ARQGA

CONTENTS

ARQUIVOS DE GASTROENTEROLOGIA
ARCHIVES OF GASTROENTEROLOGY
v. 57 Nº 2 Abr/Jun 2020

EDITORIAL

ORIGINAL ARTICLE

REVIEW

E-VIDEO

ERRATUM

INSTRUCTIONS TO AUTHORS

Scope and policy

The **Archives of Gastroenterology** publishes originals and unseen contributions, from national and foreign researchers, compatible with the goals of the journal and suited to the scientific and editorials standards.

The submission of the manuscript implies that the work in full or part it has not been published in another source or means of communication and not under review in another journal for publication.

Only Original studies, from clinical or surgical nature, new techniques, epidemiology studies and Review article are accepted. Case reports are not published. The Original Article sections are: Endoscopy, Surgery, Hepatology, Digestive Motility, Clinical Gastroenterology, Experimental Surgery, Pediatric Gastroenterology, Gastroenterological Clinical Pathology, and Nutrition. It also publishes Editorials, Letter to the Editor, Consensus, Brief Communication, Supplements and E-video.

The assessment work is done impartially and anonymous, that is, omitting to the reviewers, any identification of its origin. Original Articles are evaluated by at least two reviewers (peer review). The estimated time process is 90 days from submission. The decision about acceptance for publication is taken by the Editorial Board.

No fee is required from authors for submission, evaluation and publication of articles. The **Archives of Gastroenterology** is available online with an open and free access. It is not necessary to ask the journal for permission for electronic copy, provided that the proper credit is given to the original source.

Submissions only through the ScholarOne interface, on SciELO Portal: http://mc04.manuscriptcentral.com/ag-scielo

Archives of Gastroenterology is available online with an open and free access: http://www.scielo.br/scielo.php?script=sci_issues&pid=0004-2803&lng=en&nrm=iso

General rules

The text must be in English language. The number of authors is limited to six for Original Articles and three for Brief Communication. Exceptions can be made in the case of multicentric studies.

The word limit for Brief Communication recommended is no more than 2500; it may contain a figure and a table and the references do not exceed 15.

Articles of research involving human subjects must be marked in Methods section, expressly agreed with the ethical standards and with due informed consent of the participants. Research with human must bring the title page the number of the opinion of the Committee's approval of Research Ethics. Brazilian studies should be in accordance with Resolution 466/2012 of the National Health Council of the Ministry of Health (Brazil), which deals with the Code of Ethics for Human Research, and for studies outside Brazil, shall be in accordance with the Declaration of Helsinki.

Studies involving animals should state the agreement with international ethical principles (e.g., *Committee for Research and Ethical Issues of the International Association for the Study of Pain*, published in PAIN, 16: 109-110, 1983) and national instructions (Laws 6638 / 79, 9605/98, 24665/34 Decree) governing animal research and bring the number of the opinion approved by the Ethics Committee on Animal Research.

For clinical trials, the presentation of the clinical trial registration number on the Methods is mandatory. The complete list of all clinical trials registries can be found at: http://www.who.int/ictrp/network/primary/en/index.html.

It is recommended a cover letter with the intention in publish on the **Archives of Gastroenterology**, highlighting the importance of this publication and research. This letter must be written in the "Author's Cover Letter" field in the online submission.

By determination of SciELO, the adoption of orcid as an identifier of the authors will become mandatory from January 2019.

Format

The submitted manuscript must be sent in Microsoft Word format and organized as follows:

1) Title in English and Portuguese; for foreign authors the translation will be done.
2) Authors names; do not insert staff positions or similar adjectives.
3) For each author should be described his participation in the study. (e.g. data collection, survey execution, writing of text, statistical analysis and so on).
4) The department and institution where the work was performed.
5) Orcid from all authors.
6) Acknowledgement of grants and other financial support. Interest of conflicts must be declared or not if so. If so, sponsors must be declared.
7) Structured Abstract (Background, Objective, Methods, Results, Conclusion) - The papers should be sent in English and Portuguese (200–600 words); abbreviations, footnotes and references should be avoided; for foreign authors the translation will be done.
8) Headings (3 to 10). Always use terms of Medical Subject Headings (MeSH) list from MEDLINE. Available from: http://www.nlm.nih.gov/mesh/meshhome.html
9) We strongly recommend this paper division: Introduction; Methods; Results; Discussion; Conclusion; Acknowledgements.
10) All contributors who do not meet the criteria for authorship may be mentioned in Acknowledgments.
11) References - **Archives of Gastroenterology** adopts the Vancouver format. Complete text in: https://www.nlm.nih.gov/bsd/uniform_requirements.html Cite references in the text using Arabic numerals in the order of appearance, within parentheses. Do not arrange the list alphabetically. For up to six authors, list all authors. For more than six authors, list first six authors followed by "et al.".
12) Tables and Figures should be cited in the text in Arabic numerals. Preferably, attached separately in JPG or PNG. If they are inside the article, they should after the references. Please do not insert tables and figures in the middle of the text.

13) Tables (in Microsoft Word or Excel format) - Is called Table only when there are numeric results. Explanations and abbreviations should be placed in the footer of the table.
14) Figures - photographs, graphics and drawings must be sent in high resolution digital format (2 mb). Photos can be colored, being left to editors to decide if the publication will be in color or not. The Figures should contain a short text on the subject.

E-VIDEO

Authorship

- E-Videos may have a maximum of six authors.
- Authors names: do not insert staff positions or similar adjectives. Include the department and institution where the work was performed.
- The name, telephone number and electronic address of author to whom galley proofs and requests for reprints should be sent.

Main text

- Title in English and Portuguese; for foreign authors the translation will be done.
- Please include the following in the main text:
  - Text: no more than 400 words.
  - A video legend must be insert after the main text and must be as short as possible (maximum 40 words).

Video

- Only one video is allowed for each submission.
- Note for not appear any identification from the patient (name or institutional number for example).
- Only AVI or MP4 formats are acceptable.
- Video time should not exceed 4 minutes.
- Make sure that steps and/or main findings explained and highlighted in the video must have overlay titles.

Figures

- A maximum of six images can be submitted: Upload it separately in JPG or JPG format with at least 300 dpi. Each one must have a number and a legend.

References

- The reference rules are the same as those of articles. Please read above. No more than six and numbered and cited at the main text.

doi.org/10.1590/S0004-2803.202000000-21

COVID-19. The other side of the coin

Viebig RG. COVID-19. The other side of the coin. Arq Gastroenterol. 2020;57(2):113.

The pandemic is changing the world in many ways. There is no doubt what evils have been causing not only on people's physical health, but also on their spirit, customs, social organization and the current and as well as in the future way of living. On the other hand, it has sharpened the curious spirit of physicians and researchers in the search for treatment solutions, such as vaccines, antiviral drugs and solutions to control the contagion of this and future events. Terms such as social isolation, lockdown, curve flattening, are part of family and social conversations. Social networks are full of information. Because of social isolation, conversations via apps are intense. False information, technical information, epidemiological concepts, research methods and dissemination of statistics burst like popcorn and there is countless information we receive every day. Many controversial and others completely opposed.

A scientific journal representing the gastroenterological community of Brazil, Latin American countries and other emerging countries, had a noteworthy change since March of this year: a significant increase in submissions (50%), until the month of May, compared to previous years[1].

To interpret this fact, I could not resort to a specific questionnaire, but I would like to share an imaginative exercise. Some hypotheses for this phenomenon arose: First, the pandemic allowed more time for papers that were hibernating, to be reactivated and submitted. Second, with more time left due to the decrease in didactic activities, there was a redirection of these to the production of data and texts. A third hypothesis would be that the researcher and his collaborators who in their daily activity are slaves of time, when they were free of other physical and face-to-face tasks, were able to produce intellectual work and conduct research that was projected or that emerged from the moment their thought became free from other attributions.

Anyway, I feel happy as an editor, to see this productivity increasing. I'm worried there won't be a hangover and scientific production will decline. I believe that the new NORMALITY will not allow this setback.

The world has awakened to the importance of science in every way. There was no forecasted calculations for a pandemic like this. There were not enough studies for the treatment and containment of a virus like this, despite previous epidemics such as SARS, ebola, etc. There are many problems still in the world that require active and dedicated researchers.

There is a huge effort of governments to establish strategies to care for the population, from the simplest symptoms, to cases that require technological complexity and specialized professional knowledge in view of the severity condition of the patient. May these warnings will be maintained and that this pandemic will serve as a lesson in what humanity's priorities are. The structures set up for the care of the population be absorbed by health systems around the world, because there was not even a nation that did not have to readjust.

Finally, it is hoped that the sum of efforts resulting from all these actions can produce knowledge and that it be made available to all. May the truths be told and the lies quickly wiped out. May the interests of the human race be above individual interests or the exercise of power. That the researcher's work is valued and, that they have possibilities to produce better and that they have freedom to disseminate their discoveries and doubts, producing an exchange of knowledge, (just as we are doing), good or bad, through social networks or the like.

For our part, we will continue linked to the ideas proposed by the editors, reviewers and collaborators of this journal: to disseminate science in a complete way, with open access and at no cost to the researchers. This is the mission of the **Archives of Gastroenterology** and their maintaining entities, Hospital IGESP and Brazilian Institute for Studies and Research in Gastroenterology (IBEPEGE).

Ricardo Guilherme VIEBIG

Viebig RG. COVID-19. O outro lado da moeda. Arq Gastroenterol. 2020;57(2):113.

REFERENCE

1. Scimago Journal & Country Rank. [Internet]. [Access 2020 May 24]. Available from: https://www.scimagojr.com/journalsearch.php?q=28247&tip=sid&clean=0

Corresponding author: Ricardo Guilherme Viebig. Hospital IGESP, Motilidade Digestiva e Neurogastroenterologia (MoDiNe), São Paulo, SP, Brasil. ORCID: 0000-0002-6541-0401. E-mail: rviebig@gmail.com

ORIGINAL ARTICLE

AG-2019-119
doi.org/10.1590/S0004-2803.202000000-22

Nutritional status, quality of life and life habits of women with irritable bowel syndrome: a case-control study

Ana Paula Monteiro de **MENDONÇA**[1], Luciana Miyuki **YAMASHITA**[1], Esther Dantas **SILVA**[1], Isabela **SOLAR**[1], Larissa Ariel Oliveira **SANTOS**[1] and Ana Carolina Junqueira **VASQUES**[1,2]

Received: 22 August 2019
Accepted: 17 January 2020

ABSTRACT – **Background** – Irritable bowel syndrome is a functional and chronic gastrointestinal disorder that may cause abdominal pain and altered bowel habits, affecting the nutritional status and quality of life of its carriers. Its prevalence is high, affecting about 10% to 15% of the general population in developed countries, being more prevalent in women than in men in the proportion 2:1. **Objective** – The aim of our study was to compare the profile of body adiposity, life habits, and the quality of life of women with irritable bowel syndrome with a healthy control group. **Methods** – Case-control study on 70 women, 34 with irritable bowel syndrome and 36 healthy. We applied the "Irritable Bowel Syndrome Quality of Life Questionnaire" to assess quality of life. Body adiposity was assessed from body mass index, waist circumference, and waist-to-hip ratio. We investigated the self-reporting of gastrointestinal symptoms with food deemed as problematic for carriers of irritable bowel syndrome and the presence of typical comorbidities. Assessment of life habits included: practice of physical activities, alcoholism, smoking, daytime sleepiness, and exclusion of foods from the feeding routine. For statistical analysis we used the IBM SPSS program, with a significance level at 5%. **Results** – There was higher volume of central and general adiposity in the case group compared with the control group ($P<0.05$). Cases presented a higher chance of developing IBS-related comorbidities ($P<0.05$). About of 80% of patients with irritable bowel syndrome have excluded some food from the diet ($P<0.01$) and the total amount of troublesome foods varied from 7 to 21 ($P<0.01$). The case group featured worse quality of life compared with the control ($P<0.05$). **Conclusion** – Compared to the control group, women with irritable bowel syndrome showed greater body adiposity, higher frequency of comorbidities, greater restriction on the consumption of problematic foods and worse quality of life.

HEADINGS – Irritable bowel syndrome. Adiposity. Life style. Quality of life.

INTRODUCTION

Irritable bowel syndrome (IBS) is a functional, chronic, and often disabling gastrointestinal disorder, characterized by change in bowel habits including diarrhea, constipation, pain and/or discomfort, flatulence and distension[1,2]. Its prevalence is high, affecting about 10% to 15% of the general population in developed countries, being more prevalent in women than in men in the proportion 2:1[2,3].

In Western countries, IBS is associated with worse quality of life (QOL), economic impact on work absenteeism, and productivity lost, resulting in an average annual spending of billions of dollars on medical assistance[1,2]. Patients with IBS feature significant impact on health-related QOL, particularly concerning energy/fatigue, functional limitations due to physical health problems, bodily pain, and overall perception of health[4]. Both gastrointestinal symptoms and psychiatric comorbidities (anxiety and depression) independently contribute to the decreased QOL of these patients[5]. The patients' fear of gastrointestinal symptoms having adverse consequences is also a predictive of impaired QOL and increased distress[6].

Obesity is a possible comorbidity of IBS, since intestinal motility, subclinical inflammation, diet, and gut microbiota may be interrelated[7,8]. Over the last decade, some studies aimed to find associations between body adiposity, gastrointestinal symptoms, and IBS[9-17]. Nagasako et al.[9] identified high frequencies of excess weight in patients with IBS. For bariatric patients with IBS, an improvement of IBS symptoms was demonstrated with weight reduction after the bariatric surgery intervention[13]. Authors of a recent study on morbid-obesity patients submitted to moderate caloric restriction identified improve in gastrointestinal symptoms of IBS after weight loss[14]. However, other studies did not find higher risk of IBS in obese subjects and this association is still inconclusive[15-18].

In addition, the consumption of some foods can exacerbate gastrointestinal symptoms of IBS. Main foods regarded as troublesome are sources of carbohydrates that are highly fermentable and of low absorption in the intestine, which include fructose in excess of glucose, lactose, oligosaccharides, and polyols, the so-called FODMAPs acronym[19,20]. Other troublesome foods for IBS carriers may be spicy foods, greasy foods, sources of biogenic

Declared conflict of interest of all authors: none
Disclosure of funding: Financial support from the National Council for Scientific and Technological Development (CNPq) and São Paulo Research Foundation – FAPESP process no. 15/24918-2 and 15/24920-7.
[1] Universidade de Campinas (UNICAMP), Faculdade de Ciências Aplicadas, Campinas, SP, Brasil. [2] Universidade de Campinas (UNICAMP), Gastrocentro, Laboratório de Investigação em Metabolismo e Diabetes (LIMED), Campinas, SP, Brasil.
Corresponding author: Ana Paula Monteiro de Mendonça. E-mail: ana.pmdm@hotmail.com

amines, lectins, and preservatives as well as foods that can trigger the endogenous secretion of histamine[21]. However, the self-reported frequencies for each of these groups in IBS is not well understood.

Few authors have investigated the role of life habits in the development and symptoms of IBS. In a case-control study, the pattern of alcoholic beverages consumption did not differ between patients with IBS and those from the healthy control group, and mild and moderate drinking were poorly associated with gastrointestinal symptoms[22]. On the other hand, the excessive consumption of alcoholic beverages been strongly associated with gastrointestinal symptoms in patients with IBS when compared with controls[22]. Regarding the use of tobacco, in a recent systematic review carried out by Sirri et al.[23], the authors could not state a significant statistical association with IBS. Different impairments among studies and the lack of prospective studies hindered the generalization and comparability between them[23]. Regarding sleep and physical exercise, was demonstrated that sedentary individuals are 3.5 times more likely to suffer from IBS symptoms than those who were physically active[24]; in parallel, those with good quality of sleep were 0.13 times less likely to be affected with IBS symptoms than those with sleep impairment[24].

Due to the great challenge that IBS became to health professionals and the remaining gaps in relation to its clinical-behavioral handling, our objective was to investigate associations between quality of life, body adiposity, self-reporting of gastrointestinal symptoms concerning troublesome foods, and life habits of patients with IBS, compared with a group of healthy individuals.

METHODS

Ethical considerations

Our study was approved by the Research Ethics Committee of the University of Campinas (protocol no. CAAE – 64341316.0.0000.5404). An Informed Consent Form was individually presented and read to all research volunteers. All evaluations were carried out only upon the volunteers' acceptance and signature.

We have acquired the informed consent after indicate all possible physical and psychological damages on subjects and/or their guardians before the experiment is conducted, in accordance with the Declaration of Helsinki.

Study design and casuistry

Case-control study design, with two convenience samples, being one sample composed of 34 women with IBS, namely the case group, and other sample with 36 healthy women, namely the control group. It was evaluated women aging between 20 and 59 years. Such sample was chosen because of the greater prevalence of IBS in women compared with men[25].

The case group was composed of patients with IBS who have been selected from the Specialized Outpatient Clinic (*Ambulatório Médico de Especialidades* – AME) of Limeira, in the state of São Paulo, Brazil; and from the Gastroenterology Outpatient Clinic (*Ambulatório de Gastroenterologia*) of *Hospital de Clínicas* – UNICAMP, located in the city of Campinas, state of São Paulo, Brazil.

The control group was composed of individuals from the community of the cities of Limeira and Campinas – São Paulo, Brazil. Healthy volunteers were evaluated in the Laboratory of Nutritional Assessment (LANUT) of the School of Applied Sciences – UNICAMP, and in the Laboratory of Investigation on Metabolism and Diabetes (LIMED), located on the campus of University of Campinas.

Inclusion criteria for the control group were women, aged between 18 and 59 years, stable weight over the last six months (change of up to 5% in body weight), body mass index (BMI) <30 kg/m^2, without changes in diet for the last six months. Exclusion criteria for the control group were: pregnancy, patients with other diseases that affect the nutritional status and dietary intake (diabetes, dyslipidemias, cancer, AIDS, diseases of the gastrointestinal tract such as intestinal malformation, short bowel syndrome, irritable bowel syndrome, celiac disease, lactose intolerance, inflammatory bowel disease, and Crohn's disease), and neurological disorders affecting cognition and ability to answer the questions.

Inclusion criteria for the case group were women, aging between 18 and 59 years, confirmed diagnosis of IBS according to the ROME III criteria, and not being under nutritional monitoring. Exclusion criteria for the case group were pregnancy, diseases that affect the nutritional status, and dietary intake, and neurological status.

Anamnesis

It was collected information on personal medical history and family history concerning gastrointestinal-related diseases such as fibromyalgia, chronic fatigue syndrome, temporomandibular joint dysfunctions, chronic pelvic pain, ulcer dyspepsia, and use of laxatives and antidiarrheal medications.

Life habits

The level of physical activity was assessed by the International Physical Activity Questionnaire (IPAQ)[26]. We applied a questionnaire on smoking, which has been classified as follows: smoker (smoked ≥100 cigarettes during life and currently smokes), former smoker (smoked ≥100 cigarettes and no longer smokes), and non-smoker (smoked <100 cigarettes the whole life)[27]. The consumption of alcoholic beverages was assessed in drinks as follows: less than 1 drink per month; 1 to 4 drinks per month; 5 to 7 drinks per month; and more than seven drinks per month[27]. Sleep was assessed based on the Epworth Sleepiness Scale, translated and validated to the Portuguese version[28]. We also questioned participants as for the presence of gastrointestinal symptoms in 42 foods deemed troublesome for IBS carriers[29].

Evaluation of quality of life

The "Irritable Bowel Syndrome Quality of Life Questionnaire" (IBS-QOL) was applied to evaluate quality of life using the translated version into Portuguese language. The IBS-QOL is an instrument composed of 34 items developed and validated for measuring health-related quality of life of patients with IBS. Its assessment comprises eight domains: dysphoria, interference with activity, body image, health concerns, food prevention, social reaction, sexuality, and relationships. The score of responses ranges from 1 to 5, resulting in an overall score of QOL and in each domain. Values close to 100 represent a better quality of life, while results close to 0 are related to the worst quality of life of patients with IBS[30].

Anthropometric assessment

Evaluation of weight occurred using a weighting scale (Welmy® W200) of 200-kg maximum capacity. Volunteers were standing, barefoot, with arms extended to the side of their bodies, and wearing light clothes for a proper measurement. Height was measured by a wall mount stadiometer. Body mass index was calculated and classified according to the criteria of the World Health Organization[31].

For measurement of waist circumference, patients were standing naked at the site of measurement, which occurred at the umbilical level. It was used a non-extensible measuring tape, and the reading was performed at the end of expiration. For the hip circumference, tape circled hip in the region of greater perimeter between the waist and the thigh[32]. We calculated the waist-to-hip ratio.

Statistical analysis

For statistical analysis we used the IBM SPSS program version 21.0. Average and standard deviation were used for describing parametric data, whereas medians and interquartile range were used for describing nonparametric data. Categorical data were presented in percentage values. We used the Kolmogorov-Smirnov test to evaluate the normality of the distribution of the studied variables. We used Student's *t*-test and Mann-Whitney test for comparing the two independent groups according to the normality of variables. Chi-square test was used to investigate the presence of associations between categorical variables. We calculated odds ratio for presence of diseases between cases and controls. The adopted significance level as a basis for decision was less than 5% ($P<0.05$).

RESULTS

Age and body adiposity

In TABLE 1 we can observe that the average age in both groups are within the same age group – middle-aged adults. There was significant difference in waist circumference ($P=0.043$) and hip circumference ($P=0.043$), evidencing greater metabolic diseases risk in the case group compared with the control group. However, when analyzing waist-to-hip ratio, there was no significant difference ($P=0.423$) between the groups. Since waist circumference and hip circumference are proportionately higher in the case group, there was no significant statistical difference for waist-to-hip ratio compared with controls. When analyzing BMI ($P=0.005$), we can observe overweight in the case group while in the control group we observe eutrophy.

TABLE 1. Comparison of age and profile of body adiposity for controls and cases.

Variables	Research group		*P* value
	Controls	Cases	
Age (years)	40±9	46±12	0.026[a]
IBS diagnosis time (years)	–	6±5	–
BMI (kg/m²)	24.7±2.8	28.4±6.7	0.005[a]
Waist circumference (cm)	85.4±8.7	92.1±16.6	0.043[a]
Hip circumference (cm)	100.9±9.4	106.1±11.5	0.043[a]
Waist-to-hip ratio	0.84±0.07	0.86±0.1	0.423[a]

Values are presented as mean ± SD (range). [a]Student's *t*-test. IBS: irritable bowel syndrome; BMI: body mass index.

Associated comorbidities and use of medicines

The case group showed the highest frequency of comorbidities associated with IBS when compared with the control group; $P<0.05$ (TABLE 2). In the odds ratio analysis it was identified greater chance for the development of these diseases in the case group compared with the control group. There was no significant difference in the frequency of ulcer dyspepsia ($P=0.47$) and use of laxatives among groups ($P=0.06$). Nevertheless, the cases presented a higher use of antidiarrheals compared with the control group ($P=0.008$).

TABLE 2. Frequency of presence of self-reported diseases and use of medicines for controls and cases.

Variables	Research group		*P* value	Odds ratio
	Controls n (%)	Cases n (%)		
Fibromyalgia	1 (2.8)	13 (38.2)	0.001[a]	21.6 (2.6–177.7)
Chronic fatigue syndrome	1 (2.8)	13 (38.2)	0.001[a]	21.6 (2.6–177.7)
Temporomandibular joint dysfunctions	5 (13.9)	19 (55.9)	0.001[a]	7.8 (2.4–25.1)
Chronic pelvic pain	2 (5.6)	20 (58.8)	0.001[a]	24.2 (4.9–118.0)
Ulcer dyspepsia	0 (0.0)	2 (5.9)	0.140[a]	0.5 (0.4–0.6)
Use of laxatives	2 (5.6)	7 (20.6)	0.060[a]	4.4 (0.8–22.9)
Use of antidiarrheals	0 (0.0)	6 (17.6)	0.008[a]	0.4 (0.3–0.6)

Values are presented as n (%) or odds ratio (range). [a]Chi-square test.

Life habits

Variables related to life habits are presented in TABLE 3. There was no statistically significant association between smoking ($P=0.189$), daytime sleepiness ($P=0.314$) and physical activity ($P=0.82$) with IBS. The frequency of the consumption of alcoholic beverages was lower in cases compared with controls ($P=0.011$).

TABLE 3. Comparison of smoking, consumption of alcoholic beverages, sleepiness scale, and physical activity for controls and cases.

Variables		Research group		*P* value
		Controls n (%)	Cases n (%)	
Smoking	Non-smoker	31 (86.9)	27 (79.4)	0.189[a]
	Former smoker	5 (13.9)	4 (11.8)	
	Smoker	0 (0.0)	3 (8.8)	
Consumption of alcoholic beverages	< 1 drink per month	17 (47.2)	28 (82.4)	0.011[a]
	1 to 4 drinks per month	13 (36.1)	5 (14.7)	
	5 to 7 drinks per month	5 (13.9)	0 (0.0)	
	> 7 drinks per month	1 (2.8)	1 (2.9)	
Daytime sleepiness		6±5	7±5	0.314[b]
Physical activity	Low	2 (5.6)	0 (0.0)	0.820[a]
	Moderate	34 (94.4)	34 (100.0)	
	High	0 (0.0)	0 (0.0)	

Values are presented as n (%) or mean ± SD (range). [a]Chi-square test. [b]Student's *t*-test.

Troublesome foods

In TABLE 4 we show the frequency of self-reporting of 42 foods deemed troublesome causing gastrointestinal aggravations in case and control groups. Thirty-three (78.5%) foods mentioned presented more reports of worsening regarding gastrointestinal symptoms for IBS patients compared with controls ($P<0.05$). There was significant difference in the average of total amount of troublesome foods ($P<0.01$) and in the frequency of exclusion of foods ($P<0.01$) between both groups. About 80% of patients with IBS excluded some food from the diet and the total amount of troublesome foods varied from 7 to 21 for those carriers of IBS.

TABLE 4. Comparison of troublesome foods for controls and cases.

Foods	Research group		*P* value
	Controls n (%)	Cases n (%)	
Apple	1 (2.8)	8 (23.5)	0.010[a]
Pear	1 (2.8)	6 (17.6)	0.038[a]
Peach	0 (0.0)	5 (14.7)	0.017[a]
Mango	0 (0.0)	13 (38.2)	<0.01[a]
Cherry	0 (0.0)	0 (0.0)	–
Nectarine	0 (0.0)	1 (2.9)	0.300[a]
Watermelon	3 (8.3)	12 (35.2)	0.006[a]
Honey	0 (0.0)	1 (2.9)	0.300[a]
Natural juice	2 (5.6)	9 (26.5)	0.016[a]
Artichoke	0 (0.0)	0 (0.0)	–
Beet	0 (0.0)	6 (17.6)	0.008[a]
Broccoli	3 (8.3)	14 (41.2)	0.001[a]
Cabbage	8 (22.2)	21 (61.8)	0.001[a]
Okra	1 (2.8)	6 (17.6)	0.038[a]
Garlic	1 (2.8)	6 (17.6)	0.038[a]
Onion	0 (0.0)	9 (26.5)	0.001[a]
Cauliflower	4 (11.1)	11 (32.4)	0.030[a]
Industrial tomato sauce	7 (19.4)	17 (50.0)	0.007[a]
Pea	0 (0.0)	4 (11.8)	0.034[a]
Chickpeas	4 (11.1)	8 (23.5)	0.168[a]
Lentils	1 (2.8)	5 (14.7)	0.075[a]
Beans	12 (33.3)	26 (76.5)	<0.01[a]
Milk	9 (25.0)	28 (82.4)	<0.01[a]
Ice cream	3 (8.3)	19 (55.9)	<0.01[a]
Yogurt	5 (13.9)	18 (52.9)	<0.01[a]
Condensed milk	0 (0.0)	19 (52.9)	<0.01[a]
Fresh cheeses	1 (2.8)	20 (58.8)	<0.01[a]
Wheat- or rye-based foods	5 (13.9)	19 (55.9)	<0.01[a]
White bread	7 (19.4)	14 (41.2)	0.047[a]
Whole wheat bread	2 (5.6)	6 (17.6)	0.112[a]
Pasta	2 (5.6)	13 (38.2)	0.001[a]
Rice	1 (2.8)	8 (23.5)	0.01[a]
Chocolate	2 (5.6)	19 (55.9)	<0.01[a]
Fried foods	6 (16.7)	24 (70.6)	<0.01[a]
Pizza	3 (8.3)	19 (55.9)	<0.01[a]
Pies and pastries	1 (2.8)	18 (52.9)	<0.01[a]
Coffee	1 (2.8)	13 (38.2)	<0.01[a]
Alcoholic beverage	3 (8.3)	7 (20.6)	0.143[a]
Beef	4 (11.1)	15 (44.1)	0.002[a]
Pork	1 (2.8)	12 (35.3)	<0.01[a]
Chicken	0 (0.0)	5 (14.7)	0.017[a]
Fish	0 (0.0)	2 (5.9)	0.140[a]
Total amount of troublesome foods	3±3	14±7	<0.01[b]
Food exclusion from the diet	25.0	79.4	<0.01[a]

Values are presented as % or mean ± SD (range). [a]Chi-square test. [b]Student's *t*-test.

Quality of life

Quality of life was worse in case group than in the control group. There was worse quality of life for the domains dysphoria, interference with activity, body image, health concerns, food prevention, social reaction, sexuality, relationships ($P<0.01$), and in the overall quality of life ($P<0.01$) for carriers of IBS, compared with the control group (TABLE 5).

TABLE 5. Comparison of overall quality of life and of each subdomain of the questionnaire of quality of life for IBS carriers, in groups and controls.

Domains	Research group		*P* value[a]
	Controls	Cases	
Dysphoria	81.6±23.7	67.0±25.2	<0.01
Interference with activity	71.3±29.9	47.2±24.3	<0.01
Body image	70.9±29.9	50.0±25.2	<0.01
Health concerns	66.6±32.0	45.1±25.7	<0.01
Food prevention	67.1±31.3	44.8±28.0	<0.01
Social reaction	83.7±41.0	74.8±56.5	<0.01
Sexuality	81.2±24.4	64.3±33.7	<0.01
Relationships	88.0±21.6	77.2±26.9	0.001
General score of quality of life	76.4±24.1	58.7±21.7	<0.01

Values are presented as mean ± SD (range). [a]Mann-Whitney test.

DISCUSSION

In our study we investigated the profile of body adiposity, life habits, self-reporting of troublesome foods, and the quality of life of women with IBS in comparison with a healthy control group. The main findings showed that IBS patients featured more general, abdominal, and gluteofemoral adiposity; higher frequency of comorbidities and use of antidiarrheals; less consumption of alcoholic beverages; higher frequency of self-reporting of troublesome foods and food exclusion from the diet; and worse quality of life when compared with controls.

We found positive association between IBS and increased volume of android fat, according to waist circumference, and gynoid, according to hip circumference, and general fat according to BMI. In literature there are studies with controversial results concerning the association of BMI with gastrointestinal symptoms[8-12,14,15,17,33,34]. In prospective studies, Aasbrenn M et al.[14] and Sadik R[35] demonstrated that visceral adiposity and waist circumference are associated with a significant increase in the risk of IBS, in addition to the association between increased severity of IBS symptoms and increase in BMI. A diet poor in fiber, and rich in saturated fat and fermentable carbohydrates may contribute to IBS symptoms in obese individuals[8]. Moreover, high BMI is related to increased colon transit and the consequent increase in gastrointestinal symptoms. In patients with overweight, colon and rectosigmoid transit were faster compared with eutrophic patients, and symptoms of pain/discomfort and swelling are also associated with abnormalities of the colon transit in obese patients with IBS[35]. On the other hand, a study conducted by Van Oijen et al.[36] with 1023 individuals reported that BMI alone does not predict the occurrence of gastrointestinal disorders and symptoms such as abdominal pain, diarrhea, and constipation. Authors of a recent study on a large sample of patients with IBS

and control individuals demonstrated that obesity is as much often found in IBS as in the general population[37]. The fact the control group has a BMI <30 kg/m² as inclusion criterion may have favored the findings of higher adiposity in case individuals, since the population of Brazilian adult women features an obesity prevalence of 18.7%[38].

In our study, we found a statistically significant difference in the presence of comorbidities associated with IBS. IBS is commonly manifested with other chronic painful disorders, such as dyspepsia, fibromyalgia, chronic fatigue syndrome, and temporomandibular joint dysfunctions[25,39]. A systematic-review study conducted by Whitehead et al.[40] found association of IBS with other non-gastrointestinal disorders, such as fibromyalgia (49%), chronic fatigue syndrome (51%), temporomandibular joint dysfunction (64%), and chronic pelvic pain (50%), suggesting that each disorder is the manifestation of varied combinations of physiological and psychological factors that interact. The use of antidiarrheals for those carriers of IBS was significantly higher compared with healthy individuals. An alternative as a second-line treatment for gastrointestinal symptoms of IBS is using laxatives and antidiarrheals[25]. The use of laxatives can promote constipation relief with improvement in quality of life, being well tolerated in adults and children, and it may contribute to change the consistency and shape of feces[41,42].

Among the analyzed parameters regarding life habits, consumption of alcoholic beverages showed significant difference between cases and controls. Patients with IBS have intolerance to several alcoholic beverages, and generally have low consumption of such due to aggravations to gastrointestinal symptoms such as abdominal pain and diarrhea caused by the change of intestinal permeability and motility[7,22]. Advice on healthy eating and lifestyle are recommended as first-line approach in the dietary handling of IBS, and the standard recommendation is to decrease the consumption of alcoholic beverages because of its association with gastrointestinal symptoms in IBS patients[43].

Most foods deemed troublesome in literature[29] and investigated in our study were reported as triggers of gastrointestinal symptoms in IBS carriers when compared with the healthy control group. Food intolerance is a frequent problem with significant consequences for individuals with IBS. Many patients with IBS associate eating some foods (such as dairy products, wheat-based products, spicy and fried foods, fruits and vegetables) with the onset and development of IBS symptoms, and about 62% of individuals have diet restrictions or exclusion[44,45]. These foods are rich in FODMAPs and IBS individuals are often intolerable to these carbohydrates[2,45]. According Mullin et al.[2], individuals who manifest adverse reactions to foods present worse quality of life and cases of anxiety or depression associated with IBS. Diets with low levels of FODMAPs, with different proportions of proteins, fats, and carbohydrates, can improve symptoms in patients by decreasing patterns of abdominal pain and bloating, and improve quality of life in more than half of patients with IBS[2,45-47].

In our study we noted worse overall quality of life in all studied domains in IBS patients compared with healthy individuals, being food prevention and health concerns the most affected subdomains in patients with the syndrome. IBS causes reduction of quality of life with the same degree of commitment as diabetes, congestive heart failure, kidney failure, and liver cirrhosis[48]. The QOL of patients with IBS was influenced by extraintestinal symptoms, such as sexuality, mood, and anxiety, in addition to the decrease in QOL concerning energy/fatigue, limitations to perform their daily activities at work, pain, overall perception of health, inability to follow an unrestricted diet, and worsening in relationships, aggravating the functional status and well-being of patients[4,49,50]. The fear of gastrointestinal aggravations is also a predictive of impairment of QOL, increased anxiety, and social isolation[5,6]. A clinically significant change in patients with IBS is seen from the therapeutic gain of ≥14 points in the IBS-QOL[5].

Certainly, there are limitations in our study. We conducted it in a secondary/tertiary healthcare scenario, which hinders the generalization of findings to the overall IBS population. As aforementioned, the fact the control group has a BMI <30 kg/m² may have favored the findings of higher adiposity in case individuals. Finally, the final sample size was small, which made separate analyses with each IBS phenotype impossible.

Therefore, in our case-control study conducted on adult women, IBS was associated with body adiposity, chronic painful disorders, food restriction, lower consumption of alcoholic beverages, and worst quality of life compared with healthy individuals, thus suggesting a demand of multidisciplinary health care towards this population. Confirmation of these data in other population extracts would assist in the comprehensive understanding of the clinical nutritional profile of these individuals, and may support interventions and handling of IBS.

ACKNOWLEDGEMENTS

We thank Prof. Cristiane Kibune Nagasako and Prof. Ciro Garcia Montes for assistance with data collection. We would also like to thank National Council for Scientific and Technological Development (CNPq) and São Paulo Research Foundation – FAPESP for funding the study.

Authors' contribution

Conceptualization: all authors. Methodology: Yamashita LM, Solar I, Santos LAO, Vasques ACJ. Formal analysis: Mendonça APM, Vasques ACJ. Funding acquisition: Vasques ACJ. Project administration: Vasques ACJ. Visualization: Mendonça APM, Yamashita LM, Vasques ACJ. Writing – original draft: Mendonça APM. Writing – review and editing: Yamashita LM, Vasques ACJ. Approval of final manuscript: all authors.

Orcid

Ana Paula Monteiro de Mendonça: 0000-0001-5218-3791.
Luciana Miyuki Yamashita: 0000-0002-6233-1142.
Esther Dantas Silva: 0000-0001-6323-8743.
Isabela Solar: 0000-0003-3500-1567.
Larissa Ariel Oliveira Santos: 0000-0002-3663-1942.
Ana Carolina Junqueira Vasques: 0000-0001-9222-1107.

Mendonça APM, Yamashita LM, Silva ED, Solar I, Santos LAO, Vasques ACJ. Estado nutricional, qualidade de vida e hábitos de vida em mulheres com síndrome do intestino irritável: um estudo caso-controle. Arq Gastroenterol. 2020;57(2):114-20.

RESUMO – **Contexto** – A síndrome do intestino irritável é uma desordem gastrointestinal crônica e funcional que pode causar dor abdominal e alteração do hábito intestinal, afetando o estado nutricional e a qualidade de vida. Sua prevalência é alta, acomete cerca de 10% a 15% da população geral em países desenvolvidos, sendo mais prevalente em mulheres do que em homens na proporção 2:1. **Objetivo** – O objetivo deste estudo foi comparar o perfil de adiposidade corporal, os hábitos de vida e a qualidade de vida de indivíduos portadores da síndrome do intestino irritável com um grupo controle saudável. **Métodos** – Estudo caso-controle com 70 mulheres, 34 com a síndrome do intestino irritável e 36 saudáveis. Foi aplicado o *Irritable Bowel Syndrome Quality of Life Questionnaire* para avaliação da qualidade de vida. A adiposidade corporal foi avaliada a partir do índice de massa corporal, circunferência da cintura e relação cintura-quadril. Foi investigado o auto-relato de sintomas gastrointestinais de alimentos considerados problemáticos para portadores da síndrome do intestino irritável e a presença de comorbidades típicas. A análise do estilo de vida incluiu a prática de atividade física, alcoolismo, tabagismo, sonolência diurna e exclusão de alimentos. Para análise estatística foi utilizado o programa IBM SPSS, com o nível de significância de 5%. **Resultados** – Houve maior acúmulo de adiposidade central e periférica no grupo caso em comparação ao grupo controle (P<0,05). Os casos apresentaram maior chance de desenvolver comorbidades associadas à síndrome do intestino irritável (P<0,05). Cerca de 80% dos pacientes com a síndrome do intestino irritável excluíram algum alimento da dieta (P<0,01) e o total de alimentos problemáticos pode variar de 7 a 21 alimentos (P<0,01). Grupo caso apresentou pior qualidade de vida para o escore geral e para todos os domínios avaliados (P<0,05). **Conclusão** – Em comparação aos controles, as mulheres portadoras da síndrome do intestino irritável apresentaram maior adiposidade corporal, maior frequência de comorbidades, maior restrição ao consumo de alimentos considerados problemáticos e pior qualidade de vida.

DESCRITORES – Síndrome do intestino irritável. Adiposidade. Estilo de vida. Qualidade de vida.

REFERENCES

1. Ford AC, Lacy BE, Talley NJ. Irritable bowel syndrome. N Engl J Med. 2017;376:2566-78.
2. Mullin GE, Shepherd SJ, Chander BR, Ireton-Jones C, Matarese LE. Irritable bowel syndrome: contemporary nutrition management strategies. J Parenter Enteral Nutr. 2014;38:781-99.
3. Mizukami T, Sugimoto S, Masaoka T, Suzuki H, Kanai T. Colonic dysmotility and morphological abnormality frequently detected in Japanese patients with irritable bowel syndrome. Intest Res. 2017;15:236-43.
4. Gralnek IM, Hays RD, Kilbourne A, Naliboff B, Mayer EA. The impact of irritable bowel syndrome on health-related quality of life. Gastroenterologia. 2000;119:654-60.
5. Enck P, Aziz Q, Barbara G, Farmer AD, Fukudo S, Mayer EA, et al. Irritable bowel syndrome. Nat Rev Dis Primers. 2016;2:16014.
6. Lackner JM, Gudleski GD, Ma CX, Dewanwala A, Naliboff B. Representing the IBSOS Outcome Study Research Group. Fear of GI symptoms has an important impact on quality of life in patients with moderate-to-severe IBS. Am J Gastroenterol. 2014;109:1815-23.
7. El-Salhy M. Recent developments in the pathophysiology of irritable bowel syndrome. World J Gastroenterol. 2015;21:7621-36.
8. Pickett-Blakely O. Obesity and irritable bowel syndrome: a comprehensive review. Gastroenterol Hepatol. 2014;10:411-6.
9. Kibune Nagasako C, Garcia Montes C, Silva Lorena SL, Mesquita MA. Irritable bowel syndrome subtypes: Clinical and psychological features, body mass index and comorbidities. Rev Esp Enferm Dig. 2016;108:59-64.
10. Delgado-Aros S, Locke GR, Camilleri M, Talley NJ, Fett S, Zinsmeister AR, et al. Obesity is associated with increased risk of gastrointestinal symptoms: a population-based study. Am J Gastroenterol. 2004;99:1801-6.
11. Sadik R, Abrahamsson H, Ung KA, Stotzer PO. Accelerated regional bowel transit and overweight shown in idiopathic bile acid malabsorption. Am J Gastroenterol. 2004;99:711-8.
12. Ho W, Spiegel BM. The relationship between obesity and functional gastrointestinal disorders: causation, association, or neither? Gastroenterol Hepatol. 2008;4:572-8.
13. Clements RH, Gonzalez QH, Foster A, Richards WO, McDowell J, Bondora A, et al. Gastrointestinal symptoms are more intense in morbidly obese patients and are improved with laparoscopic Roux-en-Y gastric bypass. Obes Surg. 2003;13:610-4.
14. Aasbrenn M, Lydersen S, Farup PG. A Conservative Weight Loss Intervention Relieves Bowel Symptoms in Morbidly Obese Subjects with Irritable Bowel Syndrome: A Prospective Cohort Study. J Obes. 2018;2018:3732753.
15. Lee CG, Lee JK, Kang YS, Shin S, Kim JH, Lim YJ, et al. Visceral abdominal obesity is associated with an increased risk of irritable bowel syndrome. Am J Gastroenterol. 2015;110:310-9.
16. Talley NJ, Howell S, Poulton R. Obesity and chronic gastrointestinal tract symptoms in young adults: a birth cohort study. Am J Gastroenterol. 2004;99:1807-14.
17. Kubo M, Fujiwara Y, Shiba M, Kohata Y, Yamagami H, Tanigawa T, et al. Differences between risk factors among irritable bowel syndrome subtypes in Japanese adults. Neurogastroenterol Motil. 2011;23:249-54.
18. Levy RL, Linde JA, Feld KA, Crowell MD, Jeffery RW. The association of gastrointestinal symptoms with weight, diet, and exercise in weight-loss program participants. Clin Gastroenterol Hepatol. 2005;3:992-6.
19. Heizer WD, Southern S, McGovern S. The role of diet in symptoms of irritable bowel syndrome in adults: a narrative review. J Am Diet Assoc. 2009;109:1204-14.
20. Hayes P, Corish C, O'mahony E, Quigley EMM. A dietary survey of patients with irritable bowel syndrome. J Hum Nutr Diet. 2014;27:36-47.
21. Böhn L, Störsrud S, Törnblom H, Bengtsson U, Simrén M. Self-reported food-related gastrointestinal symptoms in IBS are common and associated with more severe symptoms and reduced quality of life. Am J Gastroenterol. 2013;108:634-41.
22. Reding KW, Cain KC, Jarrett ME, Eugenio MD, Heitkemper MM. Relationship between patterns of alcohol consumption and gastrointestinal symptoms among patients with irritable bowel syndrome. Am J Gastroenterol. 2013;108:270-6.
23. Sirri L, Grandi S, Tossani E. Smoking in irritable bowel syndrome: a systematic review. J Dual Diagn. 2017;13:184-200.
24. Guo YB, Zhuang KM, Kuang L, Zhan Q, Wang XF, Liu SD. Association between Diet and Lifestyle Habits and Irritable Bowel Syndrome: A Case-Control Study. Gut Liver. 2014;9:649-56.
25. Irritable Bowel Syndrome (IBS). World Gastroenterology Organization web site. http://www.worldgastroenterology.org/guidelines/global-guidelines/irritable-bowel-syndrome-ibs. Updated September 2015. Accessed August 30, 2018.
26. Matsudo S, Araújo T, Matsudo V, Andrade D, Andrade E, Oliveira L, et al. International Physical Activity Questionnaire (IPAQ): Study of validity and reliability in Brazil. Rev Bras ativ fis saúde 2001;6:5-18.
27. Ford ES, Kohl III HW, Mokdad AH, Ajani UA. Sedentary behavior, physical activity, and the metabolic syndrome among U.S. adults. Obes Res. 2005;13:608-14.
28. Bertolazi AN, Fagondes SC, Hoff LS, Pedro VD, Menna Barreto SS, Johns MW. Validation of the Epworth Sleepiness Scale in the brazilian portuguese language. Sleep. 2008;31:347-47.
29. Böhn L, Störsrud S, Törnblom H, Bengtsson U, Simrén M. Self-reported food-related gastrointestinal symptoms in IBS are common and associated with more severe symptoms and reduced quality of life. Am J Gastroenterol. 2013;108:634-41.
30. Patrick DL, Drossman DA, Frederick IO, Di Cesare J, Puder KL. Quality of life in persons with irritable bowel syndrome: development and validation of a new measure. Dig Dis Sci. 1998;43:400-11.
31. World Health Organization. Physical status: the use and interpretation of anthropometry. Geneva: WHO; 1995.
32. Cuppari L. Guideline of nutrition: clinical nutrition of adults. 2 ed. Barueri: Manole; 2005.

33. Talley NJ, Quan C, Jones MP, Horowitz M. Association of upper and lower gastrointestinal tract symptoms with body mass index in an Australian cohort. Neurogastroenterol Motil. 2004;16:413-9.
34. Talley NJ, Howell S, Poulton R. Obesity and chronic gastrointestinal tract symptoms in young adults: a birth cohort study. Am J Gastroenterol. 2004;99:1807-14.
35. Sadik R, Björnsson E, Simrén M. The relationship between symptoms, body mass index, gastrointestinal transit and stool frequency in patients with irritable bowel syndrome. Eur J Gastroenterol Hepatol. 2010;22:102-8.
36. Van Oijen MG, Josemanders DF, Laheij RJ, Van Rossum LG, Tan AC, Jansen JB. Gastrointestinal disorders and symptoms: does body mass index matter? Neth J Med. 2006;64:45-9.
37. Rusu F. Obesity and irritable bowel syndrome: coincidence or association? J Gastrointestin Liver Dis. 2018;27:205.
38. Brazil. Ministério da Saúde. Vigitel Brazil 2017: surveillance of risk and protective factors for chronic diseases by telephone survey: estimates of Frequency and sociodemographic distribution of risk and protective factors for chronic diseases in the capitals of the 26 Brazilian states and the Federal District in 2017. Available from: http://bvsms.saude.gov.br/bvs/publicacoes/vigitel_brasil_2017_vigilancia_fatores_risco.pdf.
39. Kim SE, Chang L. Overlap between functional GI disorders and other functional syndromes: what are the underlying mechanisms? Neurogastroenterol Motil. 2012;24:895-913.
40. Whitehead WE, Palsson O, Jones KR. Systematic review of the comorbidity of irritable bowel syndrome with other disorders: what are the causes and implications? Gastroenterology. 2002;122:1140-56.
41. Paré P, Fedorak RN. Systematic review of stimulant and nonstimulant laxatives for the treatment of functional constipation. Can J Gastroenterol Hepatol. 2014;28:549-57.
42. Dinning PG, Hunt L, Lubowski DZ, Kalantar JS, Cook IJ, Jones MP. The impact of laxative use upon symptoms in patients with proven slow transit constipation. BMC Gastroenterol. 2011;11:121.
43. Cozma-Petruţ A, Loghin F, Miere D, Dumitraşcu DL. Diet in irritable bowel syndrome: What to recommend, not what to forbid to patients! World J Gastroenterol. 2017;23:3771-83.
44. Monsbakken KW, Vandvik PO, Farup PG. Perceived food intolerance in subjects with irritable bowel syndrome–etiology, prevalence and consequences. 2006;60:667-72.
45. Mazzawi T, El-Salhy M. Effect of diet and individual dietary guidance on gastrointestinal endocrine cells in patients with irritable bowel syndrome (Review). Int J Mol Med. 2017;40:943-52.
46. Dolan R, Chey WD, Eswaran S. The role of diet in the management of irritable bowel syndrome: a focus on FODMAPs. Expert Rev Gastroenterol Hepatol. 2018;12:607-15.
47. Halmos EP, Power VA, Shepherd SJ, Gibson PR, Muir JG. A diet low in FODMAPs reduces symptoms of irritable bowel syndrome. Gastroenterology. 2014;146:67-75.
48. El-Salhy M. Irritable bowel syndrome: diagnosis and pathogenesis. World J Gastroenterol. 2012;18:5151-63.
49. Spiegel BM, Gralnek IM, Bolus R, Chang L, Dulai GS, Mayer EA, et al. Clinical determinants of health-related quality of life in patients with irritable bowel syndrome. Arch Intern Med 2004;164:1773-80.
50. Eswaran S, Chey WD, Jackson K, Pillai S, Chey SW, Han-Markey T. A diet low in fermentable oligo-, di-, and monosaccharides and polyols improves quality of life and reduces activity impairment in patients with irritable bowel syndrome and diarrhea. Clin Gastroenterol Hepatol. 2017;15:1890-9.

ORIGINAL ARTICLE

AG-2019-123
doi.org/10.1590/S0004-2803.202000000-41

Value of clinical, laboratory parameters and analysis of retinal vascularization in pediatric patients with portal hypertension

Mariana Batista **GONÇALVES**[1], Bruno de Queiroz **ALVES**[1], Bruna Ferraço **MARIANELLI**[1], Murilo Ubukata **POLIZELLI**[1], Ramiro Anthero de **AZEVEDO**[2,3] and Nilva Simeren Bueno de **MORAES**[1]

Received: 29 August 2019
Accepted: 27 April 2020

ABSTRACT – **Background** – Portal hypertension is one of the complications of cirrhosis and is associated with numerous systemic manifestations, including renal, brain, pulmonary, cardiac and vascular changes. In routine ophthalmological examinations performed at our service, we observed that some children diagnosed with portal hypertension had increased retinal vascular tortuosity. **Objective** – 1. To evaluate the presence of retinal vascular abnormalities (vascular tortuosity) in children diagnosed with portal hypertension; 2. To investigate the association between retinal vascular tortuosity and the presence of gastroesophageal varices in these children; 3. To evaluate the use of clinical and laboratory parameters to predict the presence of gastroesophageal varices in children with portal hypertension. **Methods** –This was a cross-sectional and observational study that included patients aged <18 years with a diagnosis of portal hypertension. The participants included were submitted to dilated fundus examination and fundus photography with Visucam (Carl Zeiss Meditec AG) device. Besides, clinical and laboratorial data were collected from the patients' medical records. **Results** – A total of 72 patients were included in this study, and 36% of them had an increase in retinal vascular tortuosity. Platelet count (P=0.001), bilirubin dosage (P=0.013) and aspartate transaminase dosage (AST) (P=0.042) were associated with the presence of gastroesophageal varices in digestive endoscopy. There was no association between retinal vascular tortuosity and the presence of gastroesophageal varices (P=0.498). **Conclusion** – The results of this study suggest that platelet count, bilirubin dosage, and aspartate transaminase dosage were associated with the presence of gastroesophageal varices in digestive endoscopy. Regarding the retinal findings, we found that there was an increase in retinal vascular tortuosity in 36% of pediatric patients, but no association was found with the presence of gastroesophageal varices.

HEADINGS – Portal hypertension. Retinal vessels. Esophageal and gastric varices. Endoscopy. Retinal diseases.

INTRODUCTION

Portal hypertension (PH) is one of the complications of cirrhosis and is associated with numerous systemic manifestations, including renal, brain, pulmonary, cardiac and vascular changes[1-4]. Among the ophthalmological findings described in this condition, we can mention xerophthalmia, keratoconjunctivitis sicca, night blindness, as well as the presence of cotton wool spots and hemorrhages in the retina[5]. In routine ophthalmological examinations performed at our service, we observed that some children diagnosed with portal hypertension had increased retinal vascular tortuosity.

In cirrhotic patients, the presence of gastroesophageal varices (GEV) indicates a severe degree of PH[6]. Esophageal varices occur in 50% of cirrhotic adult patients at diagnosis and rupture of these vascular abnormalities occurs in approximately 25% to 30% of cases. In children, the total risk of bleeding from esophageal varices is estimated at 50%, but this percentage may be higher depending on the underlying liver pathology[7].

Many studies have been conducted to identify noninvasive clinical and laboratory methods that may predict the presence of GEV in patients with portal hypertension. Preliminary data suggest that the following data may be useful in identifying adult and pediatric patients who are at increased risk of developing varicose veins: 1) Platelet count; 2) Dosage of serum albumin; 3) Presence of splenomegaly; 4) Z score of spleen size; 5) Ratio between platelet count and spleen size; 6) Mathematical model: "Clinical Prediction Rule", calculated from platelet count, Z score of the spleen and albumin dosage[8].

The objectives of this study were: 1) To evaluate the presence of retinal vascular abnormalities (vascular tortuosity) in children diagnosed with PH; 2) To investigate the association between retinal vascular tortuosity and the presence of GEV in these children; 3) To evaluate the use of clinical and laboratory parameters to predict the presence of GEV in children with PH.

METHODS

This was a cross-sectional and observational study carried out in the Departments of Ophthalmology and Hepatology of the Federal University of São Paulo (UNIFESP). The study was conducted after receiving approval from our Research Ethics Committee (number 82307718.9.0000.5505).

Declared conflict of interest of all authors: none
Disclosure of funding: no funding received
[1] Universidade Federal de São Paulo, Departamento de Oftalmologia e Ciências Visuais, Divisão de Retina e Vítreo, São Paulo, SP, Brasil. [2] Universidade Federal de São Paulo, Divisão de Cirurgia Pediátrica, São Paulo, SP, Brasil. [3] Universidade Federal de São Paulo, Divisão de Gastroenterologia Pediátrica, São Paulo, SP, Brasil.
Corresponding author: Murilo Ubukata Polizelli, MD. E-mail: murilopolizelli@gmail.com

Patients who met the following criteria were included in this study: 1) Age <18 years; 2) Regular follow-up at the Hepatology Clinic; 3) Diagnosis of portal hypertension, defined as the presence of varices at endoscopy and/or other abdominal portosystemic collaterals, splenomegaly and ascites using doppler ultrasound and computed tomography[9]; 4) Signature of the informed consent form by the participant's legal representative. The exclusion criteria were: 1) Records with incomplete data; 2) Impossibility of signing the informed consent form.

The patients included in the study were submitted to dilated fundus examination and fundus photography with Visucam (Carl Zeiss Meditec AG) device. Retinal vessel tortuosity was evaluated simultaneously in both eyes and reported as the average evaluation of the right and the left eyes. In addition, the following data were collected from the patients' medical records: age, sex, main liver disease, renal function (urea and creatinine), liver function (gamma globulin GT, alkaline phosphatase, transaminases), electrolytes (sodium and potassium), platelet count, information on the presence or absence of splenomegaly, ascites and GEV on endoscopy.

Continuous variables were given as mean ± standard deviation and categorical variables as frequencies. Categorical variables were compared by Fisher's exact test. Continuous variables were compared using the Mann-Whitney U test. Values of $P<0.05$ were considered statistically significant.

RESULTS

A total of 72 patients were included in this study. The mean age was 7.1 years (±5.2 years). Regarding the gender, 59.7% (n=43) were female and 40.3% (n=29) were male (TABLE 1).

TABLE 1. Demographic profile of the 72 patients included in the study.

Variable	
Female. N (%)	43/72 (59.7%)
Age (years)	
Mean ± SD	7.1±5.2
Median (Min–Max)	7.0 (4 days – 16 years)

Considering portal hypertension-related liver disease, 35% of study participants had biliary atresia. Others causes of PH included portal vein thrombosis, Alagille's syndrome, familial intrahepatic cholestasis, and autoimmune hepatitis (TABLE 2).

TABLE 2. Distribution of patients with portal hypertension according to the underlying liver disease.

Portal hypertension-related liver disease	
Biliary atresia	35%
Portal vein thrombosis	15%
Alagille's syndrome	8%
Progressive Familial Intrahepatic Cholestasis (PFIC)	5%
Autoimmune hepatites	4%
Others	33%

Among the 72 patients included in the study, there was an increase in retinal vascular tortuosity in 36% of cases, and this tortuosity was observed mainly in the arterial vessels (FIGURES 1 and 2).

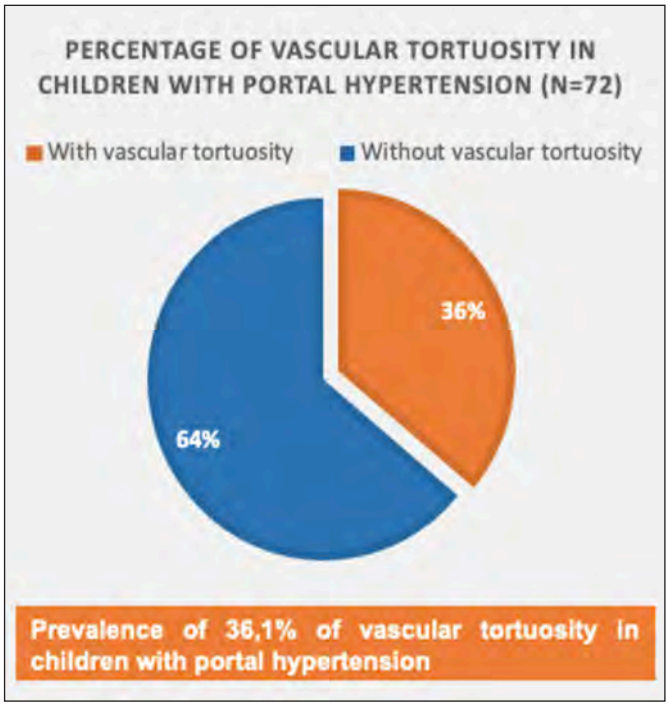


FIGURE 1. Prevalence of retinal vascular tortuosity in children with a diagnosis of portal hypertension, being followed up at the Hepatology Department.

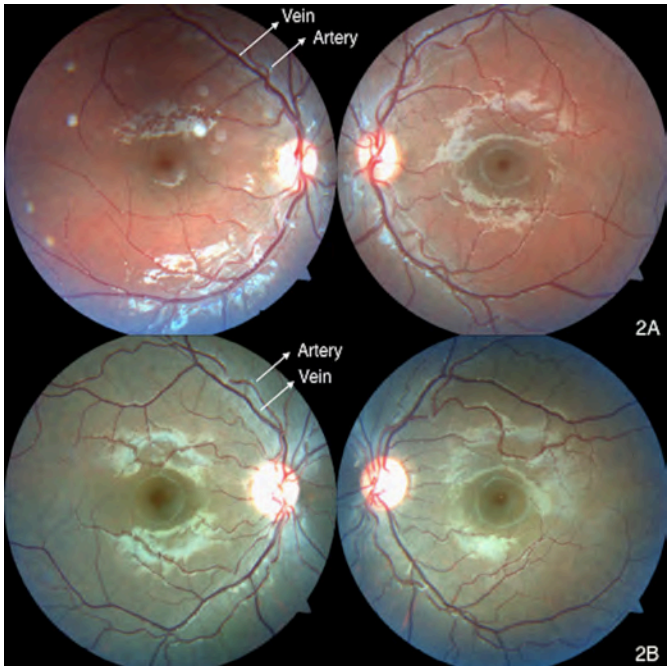


FIGURE 2. Increased retinal vascular tortuosity in patients with portal hypertension. A. A 13-year-old female patient with autoimmune hepatitis. B. Patient of 5 years, male, with liver disease.

Based on the fundus examination, fundus photography and upper digestive endoscopy examination of the study participants, an analysis to search for an association between the presence of retinal vascular tortuosity and the presence of GEV was made. In this analysis we included 40 patients who undergone endoscopy. No association was observed between these two variables (P=0.498) (FIGURE 3).

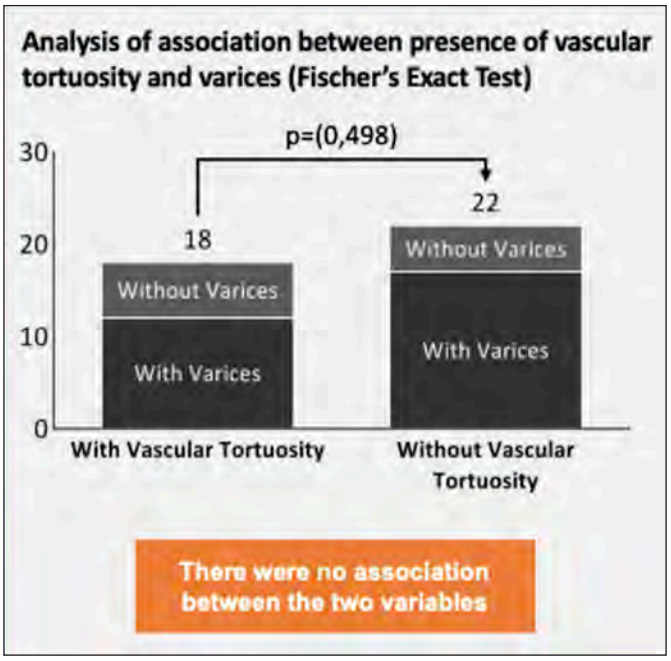


FIGURE 3. Analysis of the association between the presence of retinal vascular tortuosity in fundoscopy and gastroesophageal varices in upper digestive endoscopy.

The analysis of the association between the presence of GEV and clinical and laboratory parameters of the study participants showed that only platelet count (P=0.001), bilirubin dosage (P=0.013) and aspartate transaminase dosage (AST) (P=0.042) were associated with the presence of gastroesophageal varices in digestive endoscopy. In this analysis we included 18 participants who had undergone endoscopy and had medical records containing all the necessary laboratory and clinical data. (TABLES 3 and 4).

DISCUSSION

There are few studies in the literature about the epidemiological characteristics of pediatric patients with PH. Our study included 72 patients under 18 years of age and diagnosed with PH, among whom the average age was 7.1 years, with female predominance (59.7%).

Many conditions can cause cirrhosis in children and adolescents. In the first year of life, the most frequent causes of cirrhosis are biliary atresia and genetic and metabolic diseases. On the other hand, diseases such as autoimmune hepatitis, Wilson's disease, alpha-1-antitrypsin deficiency, and primary sclerosing cholangitis account for the majority of cases in older children[10]. In this study, 35% of cases of PH were caused by biliary atresia. Other etiologies found were portal vein thrombosis, Alagille syndrome, familial progressive intrahepatic cholestasis, among others.

TABLE 3. Evaluation of the association between laboratory parameters and the presence of gastroesophageal varices.

Variable	Without varices (n=4)	With varices (n=14)	*P*
Platelets	179250.00±25811.82	84083.33±41764.4	0.001
Total bilirubin	0.37±0.21	5.65±6.06	0.013
Direct bilirubin	0.2±0.11	4.48±5.14	0.042
Aspartate transaminase	46.75±29.74	138.33±109.41	0.042
Albumin	4.32±0.43	3.6±0.71	0.103
PELD	-2.5±6.35	6.42±10.45	0.133
INR	1.16±0.32	1.21±0.21	0.170
Alanine transaminase	47.75±40.05	113.67±112.9	0.212
Gamma GT	143.25±180.26	242.75±253.37	0.521
Creatinine	0.32±0.11	0.36±0.12	0.521
Alkaline phosphatase	453.25±285.58	547±326.34	0.684
Urea	20.5±5.45	21.25±10.64	0.862
Sodium	138.75±1.71	138.58±2.43	0.862

P: descriptive level of the non-parametric Mann Whitney. PELD: Pediatric end-stage liver disease; INR: International normalized ratio; Gamma GT: gama-glutamiltransferase.

TABLE 4. Evaluation of the association between clinical parameters and the presence of gastroesophageal varices.

	Varices		Total	*P*
	No	Yes		
	N	N	N	
Splenomegaly				0.250
No	1	0	1	
Yes	3	12	15	
Total	4	12	16	
Ascites				1.000
No	4	10	14	
Yes	0	2	2	
Total	4	12	16	

P: descriptive level of the exact Fisher's test.

There are few studies in the literature about retinal changes associated with chronic liver disease. Abe and colleagues observed retinopathy (retinal hemorrhages and cotton wool spots) in 31.8% of patients diagnosed with chronic hepatitis C. In the study conducted by Onder et al., 15.6% of patients with cirrhosis (related to hepatitis B virus or alcohol consumption) presented cotton wool spots on fundoscopy[5]. Dittmer and colleagues found 11 cases of retinopathy among the 17 cirrhotic patients included in the study: five cases of cotton wool spots, two cases of intraretinal hemorrhages and one case of papilledema. These findings disappeared or significantly decreased three months after portosystemic shunts[11]. In our study, we observed an increase in retinal vascular tortuosity in 36% of children with PH. Other changes found were intraretinal hemorrhages (one patient), disc pallor (one patient), and arteriolar narrowing (one patient). Pathophysiology involving retinopathy in cirrhosis is unknown[5].

Despite being the gold standard for the diagnosis of GEV in patients with PH, upper digestive endoscopy is an invasive, costly, and time-consuming method[6]. Thus, many studies have been conducted to establish noninvasive methods capable of predicting the presence of varicose veins in patients with chronic liver disease, as well as the risk of bleeding of these vascular abnormalities. The studies carried out so far suggest that the following methods would be able to predict the presence of GEV in adult and pediatric patients: 1) Platelet count; 2) Dosage of serum albumin; 3) Presence of splenomegaly; 4) Z score of spleen size; 5) Ratio between platelet count and spleen size; 6) Ultrasonic transient elastometry (elastography)[12]; 7) Mathematical model: "Clinical Prediction Rule", calculated from platelet count, Z score of the spleen and albumin dosage[8].

In this study, we evaluated the association of many clinical and laboratory methods with the presence of GEV in pediatric patients and observed that this association was present in the case of platelet count, bilirubin dosage, and aspartate transaminase dosage. Thrombocytopenia is a common complication in chronic liver disease and has been described in several studies as an isolated predictor of the presence of GEV in the pediatric population[8]. However, the cutoff point is not yet well established, ranging from 100,000 to 130,000 platelets[13,14]. In the study conducted by Adami and colleagues, the dosage of bilirubin and dosage of aspartate transaminase was not associated with the presence of GEV. Other studies in the literature corroborate this finding[7].

In this study, 36% of the study participants presented increased retinal vascular tortuosity. Considering the hypothesis that retinal and endoscopic vascular changes could have a similar etiopathogenesis, our research group decided to evaluate the presence of an association between these two data, since, in case of positivity, the retinal mapping could represent an essential tool for the noninvasive diagnosis of GEV. However, no statistical associations were observed between these variables.

To the best of our knowledge, this is the first study to evaluate the presence of an association between the presence of retinal vascular changes and the presence of GEV in pediatric patients with PH. Limitations of the study were the small number of participants and the subjective assessment of retinal vascular tortuosity.

CONCLUSION

In conclusion, the results of this study suggest that platelet count, bilirubin dosage, and aspartate transaminase dosage were associated with the presence of gastroesophageal varices in digestive endoscopy. Regarding the retinal findings, we found that there was an increase in retinal vascular tortuosity in 36% of pediatric patients, but no association was found with the presence of gastroesophageal varices.

Authors' contribution

Gonçalves MB: conception and design, statistical analysis, acquisition of data. Alves BQ: conception and design, acquisition of data. Marianelli BF: acquistion of data, drafting of the manuscript. Polizelli MU: analysis and interpretation of data, drafting of the manuscript. Azevedo RA, Moraes NSB: conception and design, critical revision of the manuscript. All authors have given final approval of the submitted manuscript.

Orcid

Mariana Batista Gonçalves: 0000-0003-4518-8820.
Bruno de Queiroz Alves: 0000-0001-8056-4698.
Bruna Ferraço Marianelli: 0000-0002-0141-2678.
Murilo Ubukata Polizelli: 0000-0003-2429-216X.
Ramiro Anthero de Azevedo: 0000-0002-3725-9572.
Nilva Simeren Bueno de Moraes: 0000-0001-5605-6028.

Gonçalves MB, Alves BQ, Marianelli BF, Polizelli MU, Azevedo RA, Moraes NSB. Valor de parâmetros clínicos, laboratoriais e análise da vascularização da retina em pacientes pediátricos com hipertensão portal. Arq Gastroenterol. 2020;57(2):121-5.

RESUMO – **Contexto** – A hipertensão portal é uma das complicações da cirrose e está associada a inúmeras manifestações sistêmicas, incluindo alterações renais, cerebrais, pulmonares, cardíacas e vasculares. Nos exames oftalmológicos de rotina realizados em nosso serviço, observamos que algumas crianças diagnosticadas com hipertensão portal apresentaram aumento da tortuosidade vascular da retina. **Objetivo** – 1. Avaliar a presença de anormalidades vasculares da retina (tortuosidade vascular) em crianças diagnosticadas com hipertensão portal; 2. Investigar a associação entre tortuosidade vascular da retina e presença de varizes gastroesofágicas nessas crianças; 3. Avaliar o uso de parâmetros clínicos e laboratoriais para prever a presença de varizes gastroesofágicas em crianças com hipertensão portal. **Métodos** – Estudo transversal e observacional, que incluiu pacientes com idade <18 anos com diagnóstico de hipertensão portal. Os participantes incluídos foram submetidos ao exame de fundo de olho dilatado e fotografia de fundo com dispositivo Visucam (Carl Zeiss Meditec AG). Além disso, foram coletados dados clínicos e laboratoriais dos prontuários dos pacientes. **Resultados** – Um total de 72 pacientes foi incluído neste estudo e 36% deles apresentaram aumento da tortuosidade vascular da retina. Contagem de plaquetas (P=0,001), dosagem de bilirrubina (P=0,013) e dosagem de aspartato transaminase (AST) (P=0,042) foram associados à presença de varizes gastroesofágicas na endoscopia digestiva. Não houve associação entre tortuosidade vascular da retina e presença de varizes gastroesofágicas (P=0,498). **Conclusão** – Os resultados deste estudo sugerem que a contagem de plaquetas, a dosagem de bilirrubina e a aspartato transaminase foram associadas à presença de varizes gastroesofágicas na endoscopia digestiva. Em relação aos achados da retina, descobrimos que houve um aumento na tortuosidade vascular da retina em 36% dos pacientes pediátricos, mas nenhuma associação foi encontrada com a presença de varizes gastroesofágicas.

DESCRITORES – Hipertensão portal. Vasos retinianos. Varizes esofágicas e gástricas. Endoscopia. Doenças retinianas.

REFERENCES

1. Hollenberg SM, Waldman B. The Circulatory System in Liver Disease. Crit Care Clin. 2016;32:331-42.
2. Lagi A, La Villa G, Barletta G, Cencetti S, Bacalli S, Cipriani M, et al. Cerebral autoregulation in patients with cirrhosis and ascites. A transcranial Doppler Study. J Hepatol. 1997;27:114-20.
3. Sorrentino P, Tarantino G, Conca P, Ragucci P, Perrella A. Abnormally high resistive index of central retinal artery by ultrasound color Doppler in patients with viral chronic liver disease: Correlation with worsening liver staging. Ultrasound Med Biol. 2004;30:599-604.
4. Dillon JF, Plevris JN, Wong FC, Chan KH, Lo NT, Miller Jd et al. Middle Cerebral Artery Blood Flow velocity in patients with Cirrhosis. Eur J Gastroenterol Hepatol. 1995;7:1087-91.
5. Onder C, Bengur T, Selcuk D. Relationship between retinopathy and cirrhosis. World Journal of Gastroenterology. 2005;11:2193-6.
6. Thabut D, Moreau R, Lebrec D. Noninvasive Assessment of Portal Hypertension in Patients with Cirrhosis. Hepatology. 2011;53:683-94.
7. Adami MR, Kieling CO, Ferreira CT, Santos JL, Vieira SMG. Hipertensão portal em crianças: métodos não invasivos preditores de varizes esofágicas. Boletim Científico de Pediatria. 2014;3:79-86.
8. Adami MR, Ferreira CT, Kieling CO, Hirakata V, Vieira SMG. Noninvasive methods for prediction of esophageal varices in pediatric patients with portal hypertension. World J Gastroenterol. 2013;19:2053-9.
9. Mauro E, Gadano A. What's new in portal hypertension? Liver Int. 2020;40 (Suppl 1):122-7.
10. Pinto RB, Schneider ACR, Silveira TR. Cirrhosis in children and adolescents: An Overview. World J Hepatol. 2015;7:392-405.
11. Dittmer K, Nolte W, Tondrow M, Schwörer H. Pathologic fundus changes in advanced liver cirrhosis. Reduction of symptoms after portosystemic shunt. Ophthalmologe. 1998;95:404-7.
12. Hu Z, Li Y, Li C, Huang C, Ou Z, Guo, J, et al. Using Ultrasonic Transient Elastometry (Fibroscan) to Predict Esophageal Varices in Patients with Viral Liver Cirrhosis. Ultrasound Med Biol. 2015;41:1530-7.
13. Gana JC, Turner D, Roberts EA, Ling SC. Derivation of a clinical prediction rule for the noninvasive diagnosis of varices in children. J Pediatr Gastroenterol Nutr. 2010;50:188-93.
14. Fagundes ED, Ferreira AR, Roquete ML, Penna FJ, Goulart EMA, Filho PPF, et al. Clinical and laboratory predictors of esophageal varices in children and adolescents with portal hypertension syndrome. J Pediatr Gastroenterol Nutr. 2008;46:178-83.

ORIGINAL ARTICLE

AG-2019-138
doi.org/10.1590/S0004-2803.202000000-23

Bladder and bowel dysfunction in mothers and children: a population-based cross-sectional study

Rebeca Sadigursky **RIBEIRO**, Glícia Estevam de **ABREU**, Eneida Regis **DOURADO**, Maria Luiza **VEIGA**, Victoria Andrade **LOBO** and Ubirajara **BARROSO JR**

Received: 14 September 2019
Accepted: 23 January 2020

ABSTRACT – **Background** – Recently it was shown an association between lower urinary tract symptoms in mothers and their children. However, the role of functional constipation in this binomial is unclear. **Objective** – To evaluate bladder and bowel dysfunction between mothers and children. **Methods** – A population-based cross-sectional study. Mothers and their children responded a self-administrated questionnaire composed by Rome IV criteria, International Consultation on Incontinence Questionnaire – Overactive Bladder, Dysfunctional Voiding Scoring System and demographic questions. **Results** – A total of 441 mother-child pairs was obtained. Children's mean age was 9.1±2.7 years, with 249 (56.5%) female. Mothers' mean age was 35.7±6.1 years. Isolated constipation was present at 35 (7.9%) children and 74 (16.8%) mothers. Isolated lower urinary tract symptoms were present in 139 (31.5%) children and 92 (20.9%) mothers and bladder bowel dysfunction occurred in 51 (11.6%) children and 78 (17.7%) mothers. There wasn't any association between isolated lower urinary tract symptoms in children and isolated lower urinary tract symptoms in mothers (P=0.31). In univariate analysis there were an association between bladder bowel dysfunction in children and bladder bowel dysfunction in mothers (OR=4.8 IC 95% 2.6–9.6, P<0.001) and isolated constipation in children and isolated constipation in mothers (OR=3.0 IC 95% 1.4–6.4, P=0.003). In multivariate analysis mothers with bladder bowel dysfunction was the only independent factor associated with bladder bowel dysfunction in children (OR=5.4 IC 95% 2.5–11.6, P<0.001). **Conclusion** – Mothers with bladder bowel dysfunction are more likely to have a child with bladder bowel dysfunction. Association between these two dysfunctions plays an important role in this familiar presentation.

HEADINGS – Constipation. Lower urinary tract symptoms. Child. Mothers.

INTRODUCTION

Bladder and bowel dysfunction (BBD) is present when there is co-occurrence of lower urinary tract symptoms (LUTS) and functional constipation (FC)[1]. Approximately 50% of children who seek medical attention because of LUTS have FC at the moment of consultation[1]. This is confirmed by a recent study proving that the presence of FC in children raised in 6.8 times the likelihoods of them to also present with LUTS[2]. Although BBD is a complex clinical condition because of its symptoms and its association with psychosocial problems, its physiopathology is yet to be clarified[3].

BBD can result from pelvic organs cross-sensitization; when pathological stimuli from neighboring pelvic organs lead to altered bladder functioning as urinary urgency and dysfunctional voiding[3]. The common innervation and the common embryological origin of both organs, bladder and rectum, and their anatomical proximity can explain their cross-talk[3]. Furthermore, those children presenting with FC have an increased prevalence of urgency and urinary incontinence, lower urinary tract infections, enuresis and Vesicoureteral Reflux (VUR)[4]. Also, FC treatment in those children resulted in partial or complete improvement of LUTS[4].

Many studies have demonstrated the influence of genetic and environmental factors over LUTS, such as enuresis[5]. Actually, we have demonstrated LUTS family association between mothers and children previously[6]. However, the role of FC in the analysis was not evaluated, and the influence of family history in the development of BBD is yet to be determined[6,7].

Therefore, a population-based study using validated diagnostic criteria can result in relevant information about family history of BBD, isolated LUTS (LUTS without FC) and isolated FC (FC without LUTS). The objective of the present study is to evaluate the family association between mothers and children for BBD, isolated LUTS and isolated FC.

METHODS

This is a cross-sectional study conducted in a Brazilian city from October 2016 to April 2017. Data collection was carried out in public squares and parks. Mothers were approached one by one randomly at collection points of different social-economic levels. We asked them to participate voluntarily through a self-administered questionnaire after signing the informed consent. The study was submitted to the Ethics Committee and obtained approval under the reference of CAAE 51086715.4.0000.5544.

Previously trained physicians and medical students conducted the study. The self-reported questionnaires were easy to understand, and there was no need for the questions to be read out loud, ensur-

Declared conflict of interest of all authors: none
Disclosure of funding: no funding received
Escola Bahiana de Medicina e Saúde Pública (BAHIANA), Centro de Distúrbios Miccionais na Infância (CEDIMI), Salvador, BA, Brasil.
Corresponding author: Glicia Estevam de Abreu. E-mail: gliabreu@hotmail.com

ing privacy. Mothers went to a quieter and more private location of the square or park to answer the questionnaires which were answered in about 15 minutes.

Inclusion criteria were children aged 5-14 years-old whose mothers lived with them and agreed to participate. Our exclusion criteria were (1) illiterate mothers, once questionnaires were self-administered, (2) children and mothers with neurological conditions or urinary tract or gastrointestinal malformations that could affect correct bladder functioning, and (3) mothers who did not answer the forms completely.

Questionnaires contained social-demographic information: mothers' education level, children's age, gender and ethnicity and whether the child attended a private or a public school. It also contained Dysfunctional Voiding Scoring System (DVSS) for children's LUTS whereas mothers' were asked through International Consultation on Incontinence Questionnaire – Overactive Bladder (ICIQ-OAB). ROME IV criteria (children's and adults') evaluated FC symptoms. All questionnaires were validated for the language in use[8-11].

DVSS contains ten questions including nine items concerning clinical symptoms and one item about psychosocial stress[8]. In questions one to nine, numerical answers were taken based on a Likert scale with scores from 0–3 according to the presence and severity of symptoms[8]. In the 10th item, no stressful events in the child's life meant zero points and three points if they were present[8]. Children were considered with LUTS when urinary symptoms were present at least one or two times a week: score one at items 1,2,5,6,7,8 and 9 of DVSS[8]. Items 3 and 4 were not used to define LUTS because they refer to bowel symptoms[8]. The 10th item also was kept out of the analysis because it refers to psychosocial symptoms[8].

ICIQ-OAB contains four questions about daily urinary frequency, nocturia, urinary urgency and urinary incontinence[9]. Answers were scored from 0–4 in a Likert scale also according to the presence and severity of symptoms[9]. Mothers were positive for urinary urgency or urinary incontinence when presented them at least "sometimes" (score two)[9]. Nocturia was defined as at least two micturitions at night (score two). Increased daily urinary frequency happened when mothers had nine or more micturitions a day (score two)[9]. Mothers with LUTS had either nocturia or urgency or incontinence or increased daily urinary frequency[9].

ROME IV criteria, adults' and children's, contain six questions adapted to each version[10,11]. Child/Adolescent ROME IV criteria are: (1) Two or fewer defecations in the toilet per week; (2) At least one episode of fecal incontinence per week; (3) History of retentive posturing or excessive volitional retention; (4) History of painful or hard bowel movements; (5) Presence of a large fecal mass in the rectum; (6) History of large diameter stools which may obstruct the toilet[10]. Children were constipated when they presented at least two positive criteria[10].

Adults' ROME IV criteria are: (1) Straining during at least 25% of defecations; (2) Lumpy or hard stools in at least 25% of defecations (3) Sensation of incomplete evacuation for at least 25% of defecations (4) Sensation of anorectal obstruction/blockage for at least 25% of defecations (5) Manual maneuvers to facilitate at least 25% of defecations (6) Fewer than three defecations per week[11]. Mothers were constipated when they presented at least two positive criteria[11].

According to those urinary and intestinal symptom definitions, we established the following groups:

- FC: as the group of individuals we disregarded the presence or the absence of LUTS;
- LUTS: as the group of those we disregarded the presence or the absence of FC;
- Isolated LUTS: when urinary symptoms were present in the absence of constipation;
- Isolated FC: when constipation was present in the absence of LUTS;
- BBD: when there was the co-occurrence of LUTS and FC.

Statistical analysis

We used SPSS 20.0 version for statistical analysis. The normality of numerical variables was evaluated using descriptive statistics, graphics analysis, and the Kolmogorov-Smirnov test. Numerical variables (mothers' and children's ages) were expressed as mean and standard deviation. Categorical variables (social-demographic variables, LUTS, FC, isolated LUTS, isolated FC, and BBD) were described as absolute numbers and proportions.

For the sample size calculation, we estimated a BBD prevalence of 10% in children[2]. In mothers, a higher number of FC is expected in comparison to children's population[11]; therefore, we estimated the prevalence of BBD no greater than 20%. It was necessary to estimate this percentage since there are few studies concerning BBD in adults. Then, to attain a power of 80% and a 95% confidence level, we needed a sample of, at least, 216 children and 384 mothers.

To analyze the association between numerical variables (mothers' and children's ages) and BBD in children we used t-student test. Pearson chi-square test was used to calculate the association between categorical variables: social-demographic variables and BBD in children; isolated FC in mothers and isolated FC in children; isolated LUTS in mothers and isolated LUTS in children; BBD in mothers, isolated LUTS in mothers and isolated FC in mothers and BBD in children. Associations were significant when $P<0.05$.

Afterward, all social-demographic variables and mothers' clinical characteristics (isolated LUTS, isolated FC, and BBD) were inserted into a logistic regression model in which BBD in children was the dependent variable as we tried to adjust for confounding variables. LUTS in mothers and FC in mothers were not inserted in this model because BBD in mothers is strongly correlated to them. It would interfere in the integrity of the results if they were all together in this analysis.

RESULTS

We interviewed 526 mothers and 526 children, but only 441 mother-child pairs presented their questionnaires fully answered. Children's mean age was 9.1±2.7 years-old whereas mothers' was 35.7±6.1 years-old. The mean ages did not differ significantly between groups of children with and without BBD, $P=0.80$ for children's mean age and $P=0.80$ for mothers' mean age. The study population is described in TABLE 1.

LUTS were present in 190 (43.1%) children and 170 (38.5%) mothers while FC was present in 86 (19.5%) children and 152 (34.5%) mothers. Isolated FC was observed in 35 (7.9%) children and 74 (16.8%) mothers whereas isolated LUTS were found in 139 (31.5%) children and 92 (20.9%) mothers. The co-occurrence of FC and LUTS, known as BBD, was present in 51 (11.6%) children and 78 (17.7%) mothers.

There was a positive association between mothers and children with LUTS; mothers with LUTS had 1.6 times more chance to

TABLE 1. Social-demographic characteristics of children (n=441) according to the presence of bladder and bowel dysfunction.

Variables	Children with BBD n (%)	CI 95%	Children without BBD n (%)	CI 95%	*P*-value
Gender					
Feminine	216 (55.5)	50.6–60.4	33 (63.5)	49.8–75.7	0.28
Masculine	173 (44.5)	39.6–49.4	19 (36.5)	24.3–50.2	0.28
Ethnicity					
White	75 (19.3)	15.6–23.4	10 (19.2)	10.2–31.6	0.99
Afro-American	102 (26.2)	22.0–30.8	13 (25.0)	14.7–38.0	0.85
Brown	199 (51.2)	46.2–56.1	24 (46.2)	33.0–59.7	0.50
Indigene	13 (3.3)	1.9–5.5	5 (9.6)	3.6–20.0	0.05
School attended					
Public	165 (42.4)	37.6–47.4	23 (44.2)	31.2–57.9	0.80
Private	224 (57.6)	52.6–62.4	29 (55.8)	42.1–68-8	0.80
Mothers' education level					
≤ High school	247 (63.5)	58.6–68.2	33 (63.5)	49.8–75.7	0.99
≥ Higher education	142 (36.5)	31.8–41.4	19 (36.5)	24.3–50.2	0.99

BBD: bladder and bowell dysfunction; CI: confidence interval.

have children with the same condition (OR 1.6 CI 95% 1.0–2.3, *P*=0.00). FC in mothers was also associated with FC in children; they had three times more chance to have children with FC (OR 3.0 CI 95% 1.9–4.95, *P*=0.00). Both analyses disregarded individuals with and without BBD.

Mothers with isolated FC had more children with isolated FC, *P*=0.003 (TABLE 2), although there was no association between mothers and children with isolated LUTS (TABLE 3), *P*=0.31. Also, mothers with BBD raised in 4.8-fold the chance of their children to have BBD (OR=4.8 IC 95% 2.6–9.6, *P*=0.000) (TABLE 4). Isolated FC and isolated LUTS in mothers weren't associated to BBD in children (OR=0.9 IC 95% 0.4–2.00, *P*=0.83, and OR=0.6 IC 95% 0.2–1.3, *P*=0.16, respectively) (TABLE 4).

In multivariate analysis, BBD in mothers was the only independent factor associated with BBD in children (OR=5.4 IC 95% 2.5–11.6, *P*=0.00).

DISCUSSION

This study aimed to evaluate the role of FC in the family association of LUTS, so we separated mothers and children with BBD, isolated FC, and isolated LUTS. We found positive associations between mothers and children with LUTS and between those with FC, groups in which we did not separate individuals with and without BBD. However, we only observed a positive association between mothers and children with isolated FC, but not with isolated LUTS. Also, mothers with BBD increased independently in 5.4-fold the chances of their children to have BBD.

A recent study from our research group showed a positive association of LUTS between mothers and children, although we did not evaluate the role of FC in that analysis[6,7]. Mothers with LUTS had 2.5 more chance to have children with LUTS while mothers with Overactive Bladder (OAB) had 2.8 more chance to have chil-

TABLE 2. Univariate analysis of isolated functional constipation between mothers and children.

Variables	Mothers with isolated FC n (%)	Mothers without isolated FC n (%)	OR	CI 95%	*P*-value
Children with isolated FC	12 (16.2)	22 (6)	3.0	1.4–6.4	0.003
Children without isolated FC	62 (83.8)	345 (94)			

Isolated FC: FC without LUTS; OR: odds ratio; CI: confidence interval.

TABLE 3. Univariate analysis of isolated lower urinary tract symptom between mothers and children.

Variables	Mothers with isolated LUTS n (%)	Mothers without isolated LUTS n (%)	OR	CI 95%	*P*-value
Children with isolated LUTS	33 (35.9)	108 (30.9)			
Children without isolated LUTS	59 (64.1)	241 (69.1)	1.25	0.8–2.0	0.31

Isolated LUTS: LUTS without FC; OR: odds ratio; CI: confidence interval.

TABLE 4. Frequency of children with and without bladder and bowel dysfunction according to mother's clinical characteristics.

	Mothers								
	BBD n (%)			Isolated FC n (%)			Isolated LUTS n (%)		
	with	without	*P*-value	with	without	*P*-value	with	without	*P*-value
Children with BBD	23 (29.5)	29 (8)	0.00	8 (10.8)	44 (12)	0.83	7 (7.6)	45 (12.9)	0.16
Children without BBD	55 (70.5)	334 (92)		66 (89.2)	323 (88)		85 (92.4)	304 (87.1)	

BBD: bowel and bladder dysfunction; Isolated FC: FC without LUTS; Isolated LUTS: LUTS without FC.

dren with OAB[6]. The present study, though, failed to encounter an association of isolated LUTS between mothers and children.

Other trial found that maternal urinary incontinence (UI) increased in 2.28 the likelihoods of their children to also have UI, whereas UI in fathers increased in 9.1 the likelihoods of their children to develop the same condition[12]. Likewise, children with a family history of enuresis also present with an increased risk of developing this dysfunction, mainly if both of their parents have a history of enuresis[5]. However, it is common knowledge that environmental influences can trigger LUTS in children[5,6].

These findings suggest an interaction between hereditary and environmental factors in the development of LUTS[13,14]. Most studies, though, have failed to determine gene loci related to Lower Urinary Tract Dysfunction (LUTD)[15]. One paper found an association between a polymorphism in the Arg allele of the β-adrenoreceptor (β3-AR) gene and an increased susceptibility in developing OAB[15]. Studies involving twins demonstrated that urinary incontinence, increased or decreased daily urinary frequency and nocturia were LUTS with the strongest hereditary behavior[16,17]. OAB and urinary urgency were the ones most associated with environmental influences[16,17]. Therefore, the Hereditary Component of LUTS remains uncertain.

Functional Gastrointestinal Disorders (FGID) also seem to suffer from genetic and environmental influences[7,18]. Individuals with constipated first-degree relatives have an increased chance of being constipated[7]. Chances are even higher if there are more than one case in family[7]. Children whose mothers report hard stools, encopresis and abdominal pain have more chances of also reporting the same symptomatology[18]. Furthermore, IBS which FC is one of its main clinical manifestations is commonly known to aggregate in families and affect multiple generations.

As it is for LUTD, the influence of genetic components over FC remains uncertain, and few studies tried to identify related genes, the majority of them with negative results[22]. A recent paper demonstrated lower serum motilin levels in constipated children and it was also possible to associate those serum levels of this hormone to the Bristol stool scale[23]. Other study compared the colonic epithelium of non-constipated individuals with those of patients with refractory constipation[24]. Lower numbers of Cajal cells, higher numbers of macrophages and reduced miRNA-128 expression were found in the colonic specimens from the constipated patients[24]. miRNA-128 regulates macrophages recruitment, and macrophages can cause Cajal cells death[24]. Therefore, genetics may influence the development of gastrointestinal disorders, including FC[18-25].

Despite all the recent findings, genetic factors cannot be the only responsible for these dysfunctions (gastrointestinal and urinary)[13]. Environmental influences as psychosocial stress, dietary intake, history of infections and individual microflora may also be related to BBD, isolated FC and isolated LUTS[13]. They might be responsible for the phenotypic expression of a common genotype[25-29].

The interaction between genetic and hereditary factors could explain our findings. The existence of genetic mutations would make those individuals affected by them more susceptible to these functional disorders (gastrointestinal and urinary). Then, the environment to which they would be exposed would help later to determine different clinical manifestations that exist (epigenetic). BBD and FC could be two manifestations of a common genetic mutation. We observed that BBD in mothers is an independent factor associated with BBD in children. Also, isolated FC in mothers was associated with isolated FC in children. Genetic influences over LUTS are yet to be explained.

As a limitation, this study collected only mothers' opinion about children's urinary and intestinal symptoms, which could lead to overemphasized or minimized data. However, the age range included here are mainly of children and pre-adolescents, ages in which the family still plays a significant role in their lives[30]. So, we believe that most children reported their urinary or gastrointestinal symptoms to their mothers[30]. Also, little evidence is available concerning BBD in children and adults; therefore, it is complicated to infer direct comparisons with the results found in this study. Most information came indirectly from studies about FC only or LUTS only.

CONCLUSION

BBD in mothers was an independent factor associated with BBD in children. Therefore, family history of BBD should be investigated routinely in pediatric care.

ACKNOWLEDGEMENTS

The authors are grateful to Júlia Cruz Santana, Rafaella Rabelo and Isabela da Silva Dantas for their invaluable help in the date collection.

Authors' contribuition

Substantial contributions to conception and design: Ribeiro RS, Abreu GE, Barroso Jr U, Veiga ML, Lobo VA. Acquisition of data: Dourado ER. Analysis and interpretation of data: Ribeiro RS, Abreu GE, Barroso Jr U, Veiga ML. All authors have drafted revised and approved the article.

Orcid

Rebeca Sadigursky Ribeiro: 0000-0003-2465-0318.
Glícia Estevam de Abreu: 0000-0003-3170-2294.
Eneida Regis Dourado: 0000-0001-5967-2977.
Maria Luiza Veiga: 0000-0002-3493-1642.
Victoria Andrade Lobo: 0000-0002-7160-6347.
Ubirajara Barroso Jr: 0000-0002-1067-2463.

Ribeiro RS, Abreu GE, Dourado ER, Veiga ML, Lobo VA, Barroso Jr U. Disfunção vésico-intestinal em mães e filhos: um estudo transversal de base populacional. Arq Gastroenterol. 2020;57(2):126-30.

RESUMO – **Contexto** – Recentemente foi demonstrada associação entre sintomas do trato urinário inferior entre mães e filhos. No entanto, o papel da constipação funcional neste binômio não é claro. **Objetivo** – Avaliar a disfunção vésico-intestinal entre mães e filhos. **Métodos** – Estudo transversal de base populacional. As mães e os filhos responderam a um questionário de autorresposta, composto pelos critérios de Roma IV, *International Consultation on Incontinence Questionnaire – Overactive Bladder, Dysfunctional Voiding Scoring System* e perguntas sociodemográficas. **Resultados** – Foram estudados 441 pares mãe-filho. A idade média dos filhos foi de 9,1±2,7 anos, sendo 249 (56,5%) do sexo feminino. A idade média das mães foi de 35,7±6,1 anos. A constipação sem sintomas do trato urinário inferior estava presente em 35 (7,9%) crianças e 74 (16,8%) mães. Sintomas do trato urinário inferior isolados estavam presentes em 139 (31,5%) crianças e 92 (20,9%) mães e a disfunção vésico-intestinal ocorreu em 51 (11,6%) crianças e 78 (17,7%) mães. Não houve associação entre sintomas isolados do trato urinário inferior em crianças e sintomas isolados do trato urinário inferior em mães (P=0,31). Na análise univariada, houve associação entre disfunção vésico-intestinal em crianças e disfunção vésico-intestinal em mães (OR=4,8 IC 95% 2,6–9,6; P<0,001) e constipação isolada em crianças e constipação isolada em mães (OR=3,0 IC 95 % 1,4–6,4; P=0,003). Na análise multivariada, mães com disfunção vésico-intestinal foi o único fator de associação independente para disfunção vésico-intestinal em crianças (OR=5,4 IC 95% 2,5–11,6; P<0,001). **Conclusão** – Mães com disfunção vésico-intestinal têm maior probabilidade de ter filhos com disfunção vésico-intestinal. A associação entre constipação e sintomas do trato urinário inferior desempenha um papel importante nesta apresentação familiar.

DESCRITORES – Constipação intestinal. Sintomas do trato urinário inferior. Criança. Mães.

REFERENCES

1. Burgers R, De Jong TPVM, Visser M, Di Lorenzo C, Dijkgraaf MGW, Benninga MA. Functional defecation disorders in children with lower urinary tract symptoms. J Urol. Elsevier Inc. 2013;189:1886-90.
2. Sampaio C, Sousa AS, Fraga LGA, Veiga ML, Bastos Netto JM, Barroso U. Constipation and Lower Urinary Tract Dysfunction in Children and Adolescents: A Population-Based Study. Front Pediatr. 2016;4:1-6.
3. Malykhina AP, Brodie KE, Wilcox DT. Genitourinary and gastrointestinal co-morbidities in children: The role of neural circuits in regulation of visceral function. J Pediatr Urol. Elsevier. 2017;13:177-82.
4. Halachmi S, Farhat WA. Interactions of constipation, dysfunctional elimination syndrome, and vesicoureteral reflux. Adv Urol. 2008;2008:828275.
5. Arnell H, Hjälmås K, Jägervall M, Läckgren G, Stenberg A, Bengtsson B, et al. The genetics of primary nocturnal enuresis: inheritance and suggestion of a second major gene on chromosome 12q. J Med Genet. 1997;34:360-5.
6. Sampaio AS, Fraga LGA, Salomão BA, Oliveira JB, Seixas CL, Veiga ML, et al. Are lower urinary tract symptoms in children associated with urinary symptoms in their mothers? J Pediatr Urol. 2017;13:269.e1-269.e6.
7. Chan AOO, Hui WM, Lam KF, Leung G, Yuen MF, Lam SK, et al. Familial aggregation in constipated subjects in a tertiary referral center. Am J Gastroenterol. 2007;102:149-52.
8. Calado AA, Araujo EM, Barroso Jr. U, Netto JMB, Zerati Filho M, Macedo Jr. A, et al. Cross-cultural adaptation of the dysfunctional voiding score symptom (DVSS) questionnaire for Brazilian children. Int Braz J Urol. 2010;36:458-63.
9. Pereira SB, Thiel R do RC, Riccetto C, Silva JM, Pereira LC, Herrmann V, et al. Validação do International Consultation on Incontinence Questionnaire Overactive Bladder (ICIQ-OAB) para a língua portuguesa. Rev Bras Ginecol e Obs. 2010;32:273-8.
10. Hyams JS, Di Lorenzo C, Saps M, Shulman RJ, Staiano A, Van Tilburg M. Childhood functional gastrointestinal disorders: Child/adolescent. Gastroenterology. W.B. Saunders. 2016;150:1456-1468.e2.
11. Mearin F, Lacy BE, Chang L, Chey WD, Lembo AJ, Simren M, Spiller R. Bowel Disorders. Gastroenterology. 2016 pii: S0016-5085(16)00222-5. doi: 10.1053/j.gastro.2016.02.031.
12. Von Gontard A, Heron J, Joinson C. Family history of nocturnal enuresis and urinary incontinence: Results from a large epidemiological study. J Urol. 2011;185:2303-6.
13. Olaru C, Diaconescu S, Trandafir L, Gimiga N, Stefanescu G, Ciubotariu G, et al. Some Risk Factors of Chronic Functional Constipation Identified in a Pediatric Population Sample from Romania. Gastroenterol Res Pract. 2016;2016:3989721.
14. Dehghani SM, Moravej H, Rajaei E, Javaherizadeh H. Evaluation of familial aggregation, vegetable consumption, legumes consumption, and physical activity onfunctional constipation in families of children with functional constipation versus children without constipation. Gastroenterol Rev. 2015;2:89-93.
15. Qu HC, Zhang W, Liu YL, Wang. Association between polymorphism of β3- adrenoceptor gene and overactive bladder: a meta-analysis. Genet Mol Res Mol Res. 2015;14:2495-251.
16. Wennberg A, Altman D, Lundholm C, Klint Å, Peeker R, Fall M, et al. Genetic Influences Are Important for Most But Not All Lower Urinary Tract Symptoms: A Population-Based Survey in a Cohort of Adult Swedish Twins. Eur Urol. 2011;59:1032-8.
17. Rohr G, Kragstrup J, Gaist D, Christensen K. Genetic and environmental influences on urinary incontinence: A Danish population-based twin study of middle-aged and elderly women. Acta Obstet Gynecol Scand. 2004;83:978-82.
18. Lewis ML, Palsson OS, Whitehead WE, van Tilburg MAL. Prevalence of Functional Gastrointestinal Disorders in Children and Adolescents. J Pediatr. 2016;177:39-43.e3.
19. Saito YA. The Role of Genetics in IBS. Gastroenterol Clin North Am. Elsevier Ltd; 2011;40:45-67.
20. Bonfiglio F, Nag MHA, Zheng FHT, Tigchelaar MCCE, Reznichenko FWA, Homuth NVRG, et al. A GWAS meta-analysis from 5 population-based cohorts implicates ion channel genes in the pathogenesis of irritable bowel syndrome. 2018;30:e13358.
21. Fukudo S, Kanazawa M, Mizuno T, Hamaguchi T, Kano M, Watanabe S, et al. Impact of serotonin transporter gene polymorphism on brain activation by colorectal distention. Neuroimage. Elsevier Inc. 2009;47:946-51.
22. Peeters B, Benninga MA, Hennekam RC. Childhood constipation; An overview of genetic studies and associated syndromes. Best Pract Res Clin Gastroenterol. 2011;25:73-88.
23. Ulusoy E, Arslan N, Kume T, Ulgenalp A, Cirah C, Bozkaya O, et al. Serum motilin levels and motilin gene polymorphisms in children with functional constipation. Minerva Pediatr. 2016. [Internet]. [cited 2018 Jun 9]. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27706119
24. Liu W, Zhang Q, Li S, Li L, Ding Z, Qian Q, et al. The Relationship Between Colonic Macrophages and MicroRNA-128 in the Pathogenesis of Slow Transit Constipation. Dig Dis Sci. 2015;60:2304-15.
25. Sagawa T, Okamura S, Kakizaki S, Zhang Y, Morita K, Mori M. Functional gastrointestinal disorders in adolescents and quality of school life. J Gastroenterol Hepatol. 2013;28:285-90.
26. Logan BA, Correia K, McCarthy J, Slattery MJ. Voiding dysfunction related to adverse childhood experiences and neuropsychiatric disorders. J Pediatr Urol. 2014;10:634-8.
27. Appak YÇ, Sapmaz ŞY, Doğan G, Herdem A, Özyurt BC, Kasirga E. Clinical findings, child and mother psychosocial status in functional constipation. Turkish J Gastroenterol. 2017;28:465-70.
28. Farnam A, Rafeey M, Farhang S, Khodjastejafari S. Functional constipation in children: does maternal personality matter? Ital J Pediatr. 2009;35:25.
29. Kilincaslan H, Abali O, Demirkaya SK, Bilici M. Clinical, psychological and maternal characteristics in early functional constipation. Pediatr Int. 2014;56:588-93.
30. Breinbauer C. Youth: Choices and Change. Promoting Healthy Behaviors in Adolescents. Adolescence. 2005;40:231.

ORIGINAL ARTICLE

AG-2019-150
doi.org/10.1590/S0004-2803.202000000-24

Clinical evaluation and pattern of symptoms in colorectal cancer patients

Marianne Regina Silva Potengy de **MELLO**[1], Silmara Fernandes **MOURA**[1], Camila Drumond **MUZI**[2] and Raphael Mendonça **GUIMARÃES**[3]

Received: 2 October 2019
Accepted: 20 February 2020

ABSTRACT – **Background** – Colorectal cancer is the third most common type of cancer in the world and the increased survival of the colorectal cancer population is very significant. Thus, it becomes relevant to study the symptoms associated with the progression of the disease and treatment, for proper clinical management. **Objective** – To describe the clinical and epidemiological profile of colorectal cancer patients and to identify the most prevalent signs and symptoms patterns. **Methods** – Cross-sectional study evaluating the prevalence of symptoms in 348 colorectal cancer patients admitted to a referral oncology hospital. We applied MSAS-BR scale and, through factor analysis with principal componente analysys, we performed the grouping of symptoms. **Results** – There was a predominance of men, aged 60 years or older, married, white, with high school, moderately differentiated tumor, stage III/IV disease, colon cancer and no distant metastasis. The most prevalent symptoms were weight loss (67.53%) and the least prevalent were mouth sores (2.01%). The groupings of symptoms established were "fatigue and psychic symptoms", "gastrointestinal symptoms", "self-perceptive symptoms" and "general symptoms", which described 80% of the symptoms presented. **Conclusion** – We evidenced the importance of identifying these symptoms clusters in order to improve strategies for clinical management in patients with colorectal cancer.

HEADINGS – Colorectal neoplasms. Symptom assessment. Quality of life.

INTRODUCTION

Colorectal cancer (CRC) is the third most common cancer in the world and represents the leading cause of mortality in many countries, especially in the most developed ones[1]. Importantly, it also has an increased incidence in developing countries[2]. It is estimated that in 2018 there were 1,849,518 new cases of the disease worldwide, representing 10.2% of all new cancers. In addition, the number of people who died from this cancer was 880,792, representing 9.2% of all cancer deaths in the same year[3]. In Brazil, in turn, it is estimated that there are 17,380 new cases of colorectal cancer in men and 18,980 in women for each year of the 2018-2019 biennium[4]. Finally, the average five-year survival in Brazil has increased for this location, ranging from 44.5% in the previous period to 48.3% in the most recent period[5].

There is two types of CRC: hereditary and sporadic, and the second of it is the most prevalent, and linked to the accumulation of lifelong mutations[6]. There are several evidences that lifestyle, especially diet and physical inactivity, are risk factors for sporadic colorectal cancer[2]. Classically, the disease mainly affects people over the age of 50. Therefore, the screening from this age is recommended[7]. Moreover, CRC may be asymptomatic at diagnosis or may present symptoms associated with local tumor growth[8].

Doctors and researchers generally recognized multiple symptoms separately and focus their researchers into isolated symptoms. However, Aktas[9] observed that some clusters symptom could have common mechanisms, and proposed a study about clusters that revolutionized symptom management in cancer patients. Thus, the concept of cluster symptom characterizes them as two or more concomitant symptoms that form a stable group and are relatively independent of other groupings, supported by the presence of clinical and statistical relevance, allowing a more complete description of symptom grouping in a specific context[10].

Symptoms in cancer patients vary according to a combination of factors such as cancer type, cancer diagnosis and stage, treatment modalities used and characteristics inherent to the individual, such as presence and type of comorbidities, psychosocial variables and the biological context[11].

With the increase in the incidence of colorectal cancer and the advancement of the techniques used in its treatment, surviving is more likely to achieve among patients who was treated[12], and this population group tends to increase, with greater or lesser occurrence of symptoms, according to the stage and treatment[13,14]. That said, the objectives of the present study is to characterize the pattern of symptoms in patients with colon and rectal cancer.

METHODS

This is a cross-sectional study which used a data set on the prevalence and treatment of symptoms among colorectal cancer patients treated at Brazilian National Cancer Institute (INCA), the national reference cancer treatment unit in the country.

The sample included 348 adult patients admitted to the HCI / INCA abdominal-pelvic surgery service between 2016 and 2018,

Declared conflict of interest of all authors: none
Disclosure of funding: Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq) – Bolsas de Iniciação Científica.
Research performed at: Fundação Oswaldo Cruz. Escola Politécnica de Saúde Joaquim Venâncio.
[1] Universidade Federal do Estado do Rio de Janeiro, Escola de Medicina e Cirurgia, Rio de Janeiro, RJ, Brasil. [2] Instituto Nacional de Câncer José Alencar Gomes da Silva, Rio de Janeiro, RJ, Brasil. [3] Fundação Oswaldo Cruz, Rio de Janeiro, RJ, Brasil.
Corresponding author: Raphael Mendonça Guimarães. E-mail: raphael.guimaraes@fiocruz.br

equivalent to 82% of patients admitted during this period. We included patients aged at least 18 years old who had colorectal cancer regardless of staging. Patients who had cognitive disorders assessed through the mini-mental examination or conditions that could compromise the veracity of the responses, such as neoplasia or metastasis to the CNS, were excluded from the medical records.

We performed data collection using the *Memorial Symptom Assessment Scale* (MSAS-BR), after prior information on the research objectives, agreement to participate in the study and signing of the free and informed consent form as an individual interview. Additional data were collected using a form prepared by the authors, which included sociodemographic and clinical data such as age, gender, marital status, educational level, race, primary diagnosis and presence of metastasis, use of devices and place of treatment (outpatient and inpatient).

The Memorial Symptom Assessment Scale (MSAS) is a 32-item assessment tool designed to measure the prevalence and the three associated characteristics (frequency, intensity, and distress) of the physical and psychological symptoms experienced by cancer patients in the week prior to the interview. Thus, targeted interventions can be proposed to ensure improvement in patients' quality of life[15]. MSAS-BR has good results for reliability and validity in the cancer population, as described in previous studies, with satisfactory reliability in test-retests and weighted kappa index values obtained between 0.69 and 0.96. When a symptom is experienced, the score for it is determined by the average intensity, frequency and discomfort scores, or when applicable, only by the intensity and distress scale[15,16]. It's important to mention that we approached patients at times when they were not vulnerable or in a situation that did not compromise the decision to participate in the study.

Patients were selected after the clinical staff of the National Cancer Institute's abdominal and pelvic surgery service identified the subjects eligible for the study. After this, all patients have been approached after getting basic information from their medical records. We interviewed them in a moment that it couldn't disturb clinical team examination or family visiting. It's important to highlight that most of patients were in at postoperative phase, even for evaluating the extension of disease or performing the treatment. Most of them had advanced disease, so that the diagnostic accuracy of the tumor (colon or rectum) was low at the time of investigation.

We considered means and standard deviations of symptom score to identify commonly reported symptoms. To identify symptoms that tended to occur together, we used Spearman correlations between symptom pair scores. Then, bivariate analyzes of the relationships between symptom scores and clinical and demographic variables were based on one-way analysis of variance (ANOVA) and statistically significant results were reported. As an additional measure, corresponding nonparametric analyzes were also performed using Kruskal-Wallis tests[17].

Symptom clusters were obtained using Principal Component Analysis (PCA) and Exploratory Factor Analysis (EFA). To examine any interrelationships between symptoms at each follow-up time point, principal component analysis was performed with Varimax rotation. This analytical method groups variables (symptoms) together to form a "component" (cluster), identifying which variables correlate with each other in a distinct pattern[17,18]. The highest load factor score determines the attribution of symptoms to clusters. It is noteworthy that this is the most commonly used analytical method in oncology symptom cluster research in international research. Then, the maximum likelihood method was then applied to multivariate normal data to measure the covariance between symptoms. Together, these two methods identify and determine the items (symptoms) that belong to each cluster. The SPSS v.24 statistical package was used for analysis.

Regarding the ethical aspects of this research, the study complied with the ethical and legal specifications of resolution no. 466/12 of the National Health Council/Ministry of Health, which regulates research involving human beings. Therefore, this work is authorized by INCA's Ethics and Research Committee, through its consubstantiated opinion number 863.339, not involving conflicts of interest.

RESULTS

The epidemiological profile found for the population with colorectal cancer studied was mostly male, aged 60 years or older, married, white and had high school education. They presented as predominantly colonic tumors, moderately differentiated, with stages III/IV and without distant metastases. Four clusters of colorectal cancer-related symptoms were identified: 1) fatigue and psychic symptoms; 2) gastrointestinal symptoms; 3) self-perceptive symptoms; and 4) general symptoms. The number of patients interviewed was 348, of which 55.36% (n=193) were male and 70.98% (n=247) were 60 years or older. Among the patients, 64.77% (n=225) were married, 62.67% (n=218) declared themselves white, 50.42% (n=175) had high school, 61.18% (n=213) had a moderately differentiated tumor, 54.88% (n=191) had stage III/IV disease, 61.59% (n=214) had colon cancer and 60.63% (n=211) had no distant metastasis diagnosed at the time of the interview (TABLE 1).

TABLE 1. Clinical and demographic characteristics of study sample. (n=348).

Variable	n	%
Sex		
Male	193	55.36
Female	155	44.64
Age		
Less than 60 years	101	29.02
60 years and more	247	70.98
Marital status		
Single	75	21.57
Married	225	64.77
Widow	47	13.60
Race		
White	218	62.67
Black	130	37.33
Literacy		
Illiteracy/Elemental	132	37.84
High School	175	50.42
Higher education	41	11.74
Tumor differentiation		
Well differentiated	31	8.77
Moderately differentiated	213	61.18
Poorly differentiated	36	10.37
Stage		
I/II	157	45.12
III/IV	191	54.88
Site		
Colon	214	61.59
Rectum	134	38.41
Metastasis		
Yes	137	39.37
No	211	60.63

The most prevalent symptoms in the sample were weight loss (67.53%), pain (56.61%), dry mouth (53.45%), concerns (52.30%), and panning (47.70%).). On the other hand, the least prevalent symptoms were cough (11.49%), problems urinating (10.92%), difficulty swallowing (9.77%), difficulty concentrating (6.03%) and wounds in the mouth (2.01%). The average of items in the frequency category ranged from 1.74 (mouth sores) to 2.89 (stuffing); in intensity the range was from 1.43 (difficulty concentrating) to 2.38 (constipation); and uncomfortably from 1.82 (cough) to 3.60 ("I don't look the same anymore") (TABLE 2).

As in the original instrument, it should be noted that in the MSAS-BR eight of the 32 items – such as mouth sores, hair loss and weight loss – do not appear in the frequency category because they are continuously found in the course of the disease, and not sporadic, as with the others.

When performing the multivariate analysis in the statistical package, the rotation presented in the matrices presented the grouping distribution presented in TABLE 3. Thus, the final result showed four groups of symptoms, classified as 1) fatigue and psychic symptoms; 2) gastrointestinal symptoms; 3) self-perceptive

TABLE 2. Description of symptoms in colorectal cancer patients (n=348).

Item	Prevalence	Frequency (1–4)		Intensity (1–4)		Distress (0–4)	
		Mean	SD	Mean	SD	Mean	SD
Difficulty concentrating	6.03	2.43	0.41	1.43	0.24	2.50	0.42
Pain	56.61	2.38	0.04	2.32	0.04	2.77	0.05
Lack of energy	47.41	2.58	0.06	2.12	0.05	3.06	0.07
Cough	11.49	2.00	0.18	1.44	0.13	1.82	0.17
Feeling nervous	30.17	2.28	0.08	2.19	0.08	2.84	0.10
Dry mouth	53.45	2.32	0.05	2.21	0.04	2.75	0.06
Nausea	44.54	2.28	0.05	2.29	0.05	2.92	0.07
Feeling drowsy	38.79	2.31	0.07	2.21	0.06	2.77	0.08
Numbness/tingling in hands/feet	20.69	2.40	0.12	1.95	0.10	2.46	0.12
Difficulty sleeping	39.94	2.48	0.06	2.08	0.05	2.91	0.07
Feeling bloated	47.70	2.89	0.07	2.28	0.05	3.01	0.07
Problems with urination	10.92	2.22	0.22	1.56	0.16	3.25	0.33
Vomiting	23.56	2.24	0.10	2.21	0.10	3.11	0.14
Shortness of breath	13.79	2.20	0.17	1.72	0.13	3.02	0.23
Diarrhea	12.64	2.35	0.20	1.88	0.16	2.71	0.23
Feeling sad	44.54	2.21	0.06	2.26	0.06	2.92	0.07
Sweats	11.78	2.25	0.20	1.94	0.18	2.65	0.24
Worrying	52.30	2.46	0.05	2.38	0.05	3.04	0.06
Problems with sexual interest or activity	20.40	2.20	0.11	2.06	0.10	3.33	0.17
Itching	12.93	2.00	0.17	1.73	0.14	3.13	0.26
Lack of appetite	44.83	2.48	0.06	2.37	0.06	3.02	0.08
Dizziness	20.11	2.00	0.11	1.90	0.10	3.16	0.17
Difficulty swallowing	9.77	2.75	0.31	2.30	0.26	3.42	0.38
Feeling irritable	30.17	1.74	0.07	2.15	0.08	3.05	0.12
Mouth sores	2.01			1.67	0.83	2.92	1.46
Change in the way food tastes	22.99			2.16	0.10	3.15	0.15
Weight loss	67.53			2.28	0.04	2.79	0.04
Hair loss	15.52			1.92	0.12	2.66	0.17
Constipation	29.60			2.38	0.09	3.30	0.12
Swelling of arms or legs	25.57			2.04	0.08	2.78	0.12
"I don't look like myself"	47.13			2.30	0.05	3.60	0.07
Changes in skin	31.90			2.17	0.07	3.45	0.11

symptoms; and 4) general symptoms. Each grouping of symptoms has good discriminatory capacity, represented by the eigenvalue. The group "fatigue and psychic symptoms" together describe 48.22% of the symptoms in colorectal cancer patients. The groups "gastrointestinal symptoms", "self-perceptive symptoms" and "general symptoms" describe, respectively, 15.34%, 8.04% and 6.87% of symptoms in patients with CRC. By uniting the four groups formed, there is a 78.47% characterization of symptoms presented in patients with colorectal cancer (TABLE 3).

TABLE 3. Factorial Matrix for the 4 Cluster Model in Colorectal Cancer Patients (n=348).

Cluster	Symptoms	Factorial load			
		Factor 1	Factor 2	Factor 3	Factor 4
Fatigue and psychics	Difficulty concentrating	0.778			
	Lack of energy	0.657			
	Feeling nervous	0.522			
	Feeling drowsy	0.796			
	Difficulty sleeping	0.561			
	Feeling sad	0.613			
	Worrying	0.701			
	Feeling irritable	0.514			
	Pain	0.725			
Gastrointestinal	Feeling bloated		0.692		
	Vomiting		0.617		
	Diarrhea		0.592		
	Lack of appetite		0.676		
	Difficulty swallowing		0.650		
	Constipation		0.761		
	Nausea		0.556		
Self perception	Numbness/tingling in hands/feet			0.758	
	Problems with sexual interest or activity			0.640	
	Change in the way food tastes			0.420	
	Weight loss			0.759	
	Hair loss			0.503	
	"I don't look like myself"			0.594	
	Changes in skin			0.610	
General	Cough				0.413
	Dry mouth				0.590
	Problems with urination				0.580
	Shortness of breath				0.534
	Sweats				0.657
	Itching				0.559
	Dizziness				0.660
	Mouth sores				0.556
	Swelling of arms or legs				0.496
Eigenvalue		6.031	3.485	2.317	1.193
Variance explained		48.217	15.339	8.044	6.871
Total variance explained		48.217	63.556	71.600	78.471

DISCUSSION

Colorectal cancer (CRC) patients may face a number of challenges during their treatment. In general, throughout treatment and for some time after its completion, survivors may experience multiple moderate to severe physical symptoms, including diarrhea, flatulence, changes in the frequency of bowel movement and urination, abdominal pain, nausea and vomiting, and fatigue. Although there is some consensus on time since treatment and the influence of certain factors such as staging, age and metastasis on symptoms in colorectal cancer survivors, there is limited evidence and information on the full extent of colorectal cancer symptoms and survival are fragmented[19]. For this reason, the study of symptoms has gained notoriety in recent years, especially from techniques that seek to qualify the description of its occurrence and intensity[20].

Early symptom control can help prevent complications, and especially minimize loss of quality of life, for good clinical follow-up. In fact, the occurrence of multiple independent symptoms alters the individual's functional capacity, treatment effects and quality of life when their management is inadequate. Omran et al.[21] pointed out that symptoms such as pain, dry mouth, cough, lack of appetite, drowsiness, difficulty swallowing, difficulty concentrating, concerns, lack of energy, dizziness, sadness and irritation are very relevant predictors of quality of life. life[22.23]. However, cancer symptoms and their treatment may coexist in different symptom groups.

Several studies indicate the association between colorectal cancer and changes in mental health, such as anxiety and depression[24-26]. This relationship may be influenced by specific diagnosis, disease staging, gender and age. The prevalence of depression ranges from 13% to 57% in CRC patients due mainly to the low 5-year survival rate, but also because of the use of colostomy and the effects of chemotherapy, which promote a significant reduction in the quality of life of patients[21,27]. The use of colostomy, for example, generates a great social impact on the patient's life and may be associated with reduced mental health[26].

With regard to fatigue, it is recognized that cancer-related fatigue (CRF) is one of the most frequently reported symptoms in cancer survivors. However, despite changes in body composition, with progressive deterioration of physiological functions and metabolic processes causing a decline in adaptive capacity, fatigue is often associated with psychological symptoms[27] and, therefore, it is reasonable to assume that all these symptoms remain in place at the same grouping. Thus, in the course of treating patients with RCC, it is advisable to evaluate depression and anxiety and, if necessary, refer for further diagnosis and treatment.

On the other hand, the group of "gastrointestinal symptoms" also presented significant explanatory variance value (15.34%). Marventano et al.[23] highlighted that several symptoms that occur due to cancer localization and staging, such as diarrhea, fecal incontinence, constipation, fatigue and loss of appetite are also

common and significantly impact the quality of life of patients with CRC, once that influence your daily activities and hobbies, as well as social relationships. Although there are currently several forms of intervention (clinical and surgical) for the treatment of colorectal cancer, gastrointestinal symptoms – particularly nausea, vomiting, constipation and diarrhea – continue to be prominent in the course of the disease, either by frequency or by the potential for disability. that they generate in patients[28]. Importantly, in the general population, gastrointestinal symptoms represent about 10% of complaints in routine consultations, many of them due to chronic functional conditions, such as irritable bowel syndrome, chronic constipation and benign rectal lesions[29]. Because of this, the predictive value of symptoms for screening practice is not satisfactory. However, when summarized with other variables, especially demographic, such as gender and age; and with lifestyle characteristics, such as eating habits and physical inactivity, they can contribute more substantively, not only to early detection, but mainly to the prognosis and maintenance of quality of life.

In the end, as the clusters identified in this study are usually associated with quality of life predictors, their knowledge allows a more effective management of symptoms to improve the quality of life of cancer patients through the organization of appropriate care protocols for this population[23,24]. In this regard, Schouten et al.[30], from a systematic review, highlighted the importance of the biopsychosocial impact of cancer and its treatment on the health and well-being of cancer patients. We assumed that the main focus of health care should be organized and patient-centered. Thus, it is necessary to create a more efficient therapeutic plan, even with limited health resources. Therefore, screening for psychosocial well-being and care needs encourages the detection of disorders and the referral of patients to specialized areas, contributing to the improvement of cancer patients' quality of life and making health care offered more efficient and effective.

Finally, it is important to highlight that there is no standardization of results and there is no clarity as to the content of interventions, such as instruments, procedures and conditions for implementation, which corroborates the heterogeneity found[30]. Similarly, Marventano et al.[23] evidenced the heterogeneity of instruments and different statistical analyzes used, compromising the comparison between studies.

In practice, symptom clusters are used for three main reasons. First, they may warn of unfavorable outcomes in this population, such as depression, functional limitations, poor quality of life, and mortality. Second, since we established the clusters, the evaluation of symptoms is more complete, anticipating and preventing the appearance of other related symptoms. Third, recognizing the grouping of symptoms allows greater efficiency in the management of symptoms through a single therapeutic approach, avoiding a different approach for each symptom presented by the patient[25,30]. Thus, it is necessary to carry out more studies with greater homogeneity and clarity in the methodology to allow the comparison between the studies. Still, it's important to get a sample big enough to study the cluster composition according to different type and phase of colon and rectal tumor, since they have different symptoms according to stage, for both prevalence and intensity.

CONCLUSION

The objective of the present study was to characterize the pattern of symptoms in patients with colorectal cancer. Our results are very similar to those found in other studies that evaluated patterns of symptoms in this population. We believe that the use of the instruments for symptoms evaluation seems to be useful not to manage the treatment of the disease, but to improve the quality of life.

Authors' contribution

Mello MRSP and Moura SF participated in the research execution, data collection and text writing. Guimarães RM and Muzi CD participated in the study design, statistical analysis, manuscript writing and final revision of the text.

Oricid

Marianne Regina Silva Potengy de Mello: 0000-0002-2121-5321.
Silmara Fernandes Moura: 0000-0001-9364-1656.
Camila Drumond Muzi: 0000-0002-5567-0437.
Raphael Mendonça Guimarães: 0000-0003-1225-6719.

Mello MRSP, Moura SF, Muzi CD, Guimarães RM. Avaliação clínica e padrão sintomatológico em pacientes com câncer colorretal. Arq Gastroenterol. 2020;57(2):131-6.

RESUMO – **Contexto** – O câncer colorretal é o terceiro tipo de câncer mais comum no mundo e o aumento de sobrevida da população com câncer colorretal é muito significativo. Com isso, torna-se relevante o estudo dos sintomas associados à progressão da doença e do tratamento, para um manejo clínico adequado. **Objetivo** – Descrever o perfil clínico e epidemiológico de pacientes com câncer colorretal e identificar padrões de sinais e sintomas mais prevalentes. **Métodos** – Estudo transversal que avaliou prevalência de sintomas em 348 pacientes com câncer colorretal internados em hospital de referência em oncologia. Foi aplicada a escala MSAS-BR e, através da análise fatorial com análise dos componentes principais, realizou-se o agrupamento de sintomas. **Resultados** – Houve predomínio de homens, com 60 anos ou mais, casados, de cor branca, com o ensino médio, com tumor moderadamente diferenciado, doença com estágio III/IV, com câncer de cólon e sem metástase à distância. O sintoma mais prevalente foi perda de peso (67,53%) e o menos prevalente foi ferida na boca (2,01%). Os agrupamentos de sintomas formados foram "fadiga e sintomas psíquicos", "sintomas gastrointestinais", "sintomas autoperceptivos" e "sintomas gerais", que descreveram 80% dos sintomas apresentados. **Conclusão** – Evidenciou-se a importância da identificação desses sintomas para criação de estratégias de manejo clínico de pacientes com câncer colorretal.

DESCRITORES – Neoplasias colorretais. Avaliação de sintomas. Qualidade de vida.

REFERENCES

1. Yiu AJ, Yiu CY. Biomarkers in Colorectal Cancer. Anticancer Res. 2016;36: 1093-102.
2. Dutra VGP, Parreira VAG, Guimarães RM. Evolution of mortality for colorectal cancer in Brazil and regions, by sex, 1996-2015. Arq. Gastroenterol. 2018;55:61-5.
3. International Agency for Research on Cancer (IARC). Cancer Today: Colorectal cancer [Access 2019 January]. Available from: https://gco.iarc.fr/today/data/factsheets/cancers/10_8_9-Colorectum-fact-sheet.pdf
4. Instituto Nacional de Câncer José Alencar Gomes da Silva (INCa). Estimativa 2018: incidência de câncer no Brasil. Rio de Janeiro, 2017.
5. Allemani C, Matsuda T, Di Carlo V, Harewood R, Matz M, Niksic M, et al. Global surveillance of trends in cancer survival 2000-14 (CONCORD-3): analysis of individual records for 37513025 patients diagnosed with one of 18 cancers from 332 population-based registries in 71 countries. Lancet. 2018;391:1023-75.
6. Roncucci L, Mariani F. Prevention of colorectal cancer: how many tools do we have in our basket? Eur J Intern Med. 2015;26:752-6.
7. Leggett BA, Hewett DG. Colorectal cancer screening. Intern Med J. 2015;45:6-15.
8. Saidi HS, Karuri D, Nyaim EO. Correlation of clinical data, anatomical site and disease stage in colorectal cancer. East Afr Med J. 2008;85:259.
9. Aktas A. Cancer symptom clusters: current concepts and controversies. Curr Opin Support Palliat Care. 2013;7:38-44.
10. Barsevick A. Defining the Symptom Cluster: How Far Have We Come? Semin Oncol Nurs. 2016;32:334-350.
11. Aktas A, Walsh D, Rybicki L. Symptom clusters: myth or reality? Palliat Med. 2010;24:373-85.
12. Kunitake H, Russell MM, Zheng P, Yothers G, Land SR, Petersen L, et al. Quality of life and symptoms in long-term survivors of colorectal cancer: results from NSABP protocol LTS-01. J Cancer Surviv. 2017;11:111-8.
13. Jefford M, Gough K, Drosdowsky A, Russell L, Aranda S, Butow P, et al. A Randomized Controlled Trial of a Nurse-Led Supportive Care Package (SurvivorCare) for Survivors of Colorectal Cancer. Oncologist. 2016;21:1014-23.
14. Cabilan CJ, Hines S. The short-term impact of colorectal cancer treatment on physical activity, functional status and quality of life: a systematic review. JBI Database System Rev Implement Rep. 2017;15:517-566.
15. Menezes JR, Luvisaro BMO, Rodrigues CF, Muzi CD, Guimarães RM. Confiabilidade teste-reteste da versão Brasileira do instrumento Memorial Symptom Assessment Scale para avaliação de sintomas em pacientes oncológicos. Einstein. 2017;15:148-54.
16. Rocha LF, Carvalho MS, Lacerda AAML, Viana AFV, Ramos RS, Guimarães RM, et al. Equivalência semântica da versão em português do instrumento Memorial Symptom Assessment Scale (MSAS) para avaliar sintomas em pacientes oncológicos. Rev. Bras. Pesq. Saúde. 2017;19:83-91.
17. Mingoti, SA. Análise de Dados Através de Métodos de Estatística Multivariada: uma abordagem aplicada. Belo Horizonte: Editora UFMG; 2005.
18. Wilson, M. Constructing measures. An item response modeling approach. Mahwah, NJ: Lawrence Erlbaum Associates, Publishers; 2005.
19. O'Gorman C, Stack J, O'Ceilleachair A, Denieffe S, Gooney M, McKnight M, Sharp L. Colorectal cancer survivors: an investigation of symptom burden and influencing factors.BMC Cancer. 2018;18:1022.
20. Dong ST, Costa DS, Butow PN, Lovell MR, Agar M, Velikova G, et al. Symptom Clusters in Advanced Cancer Patients: An Empirical Comparison of Statistical Methods and the Impact on Quality of Life. Journal of Pain and Symptom Management. 2016;51:88-98.
21. Omran S, Khader Y, McMillan S. Symptom Clusters and Quality of Life in Hospice Patients with Cancer. Asian Pac J Cancer Prev. 2017;18:2387-93.
22. Mattsson S, Olsson EMG, Carlsson M, Johansson BBK. Identification of Anxiety and Depression Symptoms in Patients With Cancer: Comparison Between Short and Long Web-Based Questionnaires. J Med Internet Res. 2019;21:e11387.
23. Marventano S, Forjaz M, Grosso G, Mistretta A, Giorgianni G, Platania A, et al. Health related quality of life in colorectal cancer patients: state of the art. BMC Surg. 2013;13 (Suppl 2):S15.
24. Lavdaniti M, Fradelos EC, Troxoutsou K, Zioga E, Mitsi D, Alikari V, Zyga S. Symptoms in Advanced Cancer Patients in a Greek Hospital: a Descriptive Study. Asian Pac J Cancer Prev. 2018;19:1047-52.
25. Naik AD, Uy N, Anaya DA, Moye J. The effects of age, education, and treatment on physical, sexual and body concern symptoms among multimorbid, colorectal cancer survivors. J Geriatr Oncol. 2015;6:299-306.
26. Peng YN, Huang ML, Kao CH. Prevalence of Depression and Anxiety in Colorectal Cancer Patients: A Literature Review. Int J Environ Res Public Health. 2019;16(3).
27. Agasi-Idenburg SC, Thong MS, Punt CJ, Stuiver MM, Aaronson NK. Comparison of symptom clusters associated with fatigue in older and younger survivors of colorectal cancer. Support Care Cancer. 2017;25:625-32.
28. Rangwala F, Zafar SY, Abernethy AP. Gastrointestinal symptoms in cancer patients with advanced disease: new methodologies, insights, and a proposed approach. Curr Opin Support Palliat Care. 2012;6:69-76.
29. Vega P, Valentín F, Cubiella J. Colorectal cancer diagnosis: Pitfalls and opportunities. World J Gastrointest Oncol. 2015;7:422-33.
30. Schouten B, Avau B, Bekkering GTE, Vankurunkelsven P, Mebis J, Helling J, et al. Systematics screening and assessment of psychosocial well-being and care needs of people with cancer. Cochrane Database Syst Rev. 2019;3:CD012387.

ORIGINAL ARTICLE

AG-2019-151
doi.org/10.1590/S0004-2803.202000000-25

Association between diabetics and intestinal cancer with the risk of mutation in CD38 gene in Iranian population

Mohammad **SHOKRZADEH**[1], Pouya **GOLEIJ**[2], Elmira **BEHRAVAN**[3], Nasrin **GHASSEMI-BARGHI**[1], Yaser **SALEHABADI**[1] and Abolhasan **REZAEI**[3]

Received: 2 October 2019
Accepted: 17 March 2020

ABSTRACT – **Background** – Intestinal cancer often occurs in type 2 diabetic patients. The concept of increasing insulin levels and insulin-like growth factor in the blood with type 2 diabetes are stimulated with the growth and depletion of cloned cell walls, and the continuation of this process leads to the cellular deformation. This is the evidence for intestinal cancer in type 2 diabetes in population. **Objective** – In this study, we aimed to find out the relationship between diabetics and intestinal cancer based on CD38 gene mutation. **Methods** – Samples were collected from 200 population including normal and case ones. PCR products related to rs 6449181 of CD38 gene was amplified with ARMS-PCR technique, and a 420-bp sharp banding was observed as well. According three ARMS-PCR techniques, three primers were designed by oligo7 software. Primers include F1, F2 and R (amplifying for normal, mutant and reverse primer respectively). **Results** – This band was observed using a primer F1 that carries the wild type nucleotide using a primer, and when it is used with the F2 primer, it brings the mutant primer to populations of patients with diabetes and diabetes-cancer. In addition, the clinical results including body mass index, blood glucose and insulin level were analyzed. The means ±SD and Tuckey's post hoc test were significant between the clinical characterization parameters between cases and healthy populations. The allelic gene frequencies and Hardy-Weinberg equilibrium between nucleotides were evaluated, and the significant level between the alleles and gene frequencies was observed. **Conclusion** – In general, the current study found that there is a relationship between diabetes and intestinal cancer among the studied populations.

HEADINGS – Type 2 diabetes mellitus. Intestinal neoplasms. Genotype. Genetic polymorphism.

INTRODUCTION

Type 2 diabetes is prevalent for all age groups throughout the world, and it was estimated to be 2.8% in 2000, and this percentage grew significantly to 4.4% in 2030[1]. Probably, the rate of diabetes will increase to 366 million people by 2030[1,2]. Hence, identification, taking care, education about symptoms of diabetes is necessary[2]. The current study, which we focused, is the association between type 2 diabetic and intestinal cancer. Several studies showed that there is a relationship between diabetes type 2 and human cancer, especially colorectal cancer[3,4]. Moreover, the progression of the colon tumor becomes faster when the amount of insulin in the blood gets more[5,6]. The concept of increasing insulin levels and insulin-like growth factor (IGF) in the blood with type 2 diabetes are stimulated with the growth and depletion of cloned cell walls, and the continuation of this process leads to the cellular deformation[7-9]. This is the evidence for intestinal cancer in type 2 diabetes in population[10]. At this time, we studied mutations in CD38 gene in the intestinal cancer population. CD38 is known as the cyclic ADP ribosome hydrolase. A glycoprotein that is found on the surface of many immune cells (white blood cells), including CD4+, CD8+, B lymphocytes, and natural killer cells. CD38 also acts in cell adhesion, signal transduction, and calcium signaling[11,12].

In humans, the CD38 gene located in the short arm of chromosome 4. This gene has eight exons in 15 p4, and it has a length of 70 kbp[13,14]. The genetic and autoimmune characteristics of CD38 protein are associated with diabetes. A study of the potential pathological pathways of insulin secretion by CD38 was discovered in a CD38 (Arg140Trp) gene mutation among 13% of Japanese type 2 diabetic patients with family history[15-17]. From 1990 to 2013 the rate of colorectal cancer increased by death (around 57%). The epidemiological studies suggest that diabetic mellitus especially diabetic type 2 mellitus (T2DM), associated with increased risk of cancer at several sites, including colorectal and intestinal cancer[18-20]. Furthermore, Ma et al., 2008 proposed that prostate tumors contained multiple Gleason grades as well as multiple cancer cell types that were distinguishable by their cluster designation (CD) phenotypes[21]. Generally CD38 related to risk of diabetics associated with most cancers like, the breast, liver, pancreas, Colorectal, endometrium, kidney and urinary bladder[22].

Moreover, the underlying mechanisms for a higher risk of cancer in patients with diabetes may be concerned with the insulin resistance, poor glycemic control, oxidative stress and pro-inflammatory status[23]. Studies on the intestinal cancer is very low but regarding to the same cancer, specially colorectal cancer, which was reported, the related risk factors are shared by diabetic type

Declared conflict of interest of all authors: none
Disclosure of funding: no funding received
[1] Mazandaran University of Medical Sciences, Faculty of Pharmacy, Department of Toxicology, Sari, Iran. [2] Sana Institute of Higher Education, Faculty of Biology, Department of Genetics, Sari, Iran. [3] Islamic Azad University, Faculty of Biological Sciences, Department of Genetics, Tonekabon Branch, Iran.
Corresponding author: Abolhasan Rezaei. E-mail:abolhasanrezaei70@gmail.com

2 mellitus, and the targeted organ damage may be confounders in epidemiological studies[24]. Obesity is a major risk factor for diabetic type 2 mellitus, cancer and diabetic kidney disease (DKD)[10]. In this study, we can consider two parameters including: A) is there a relationship between diabetics and CD38 gene? B) Is there a relationship between CD38 and intestinal cancer? However, studies by researchers confirmed association between diabetics and intestinal cancers; however, we focus on both the diabetic and intestinal cancer in a case what would happen about it.

METHODS

Sample preparation

The samples were provided from 200 people including 100 control cases and 100 patients from the North of Iran. (TABLE 1).

TABLE 1. Characteristics of patients and healthy controls.

Sample	Number	Age (mean)	Gender	
			Male	Female
Patient	100	55	68	32
Normal	100	50	53	47

TABLE 2. PCR program and its reaction for getting sharp band on the gel electrophoresis.

Component	Volume
Template DNA (100 ng/µL)	4.0 µL
Forward primer (10 pmol/µL)	0.5 µL
Reverse primer (10 pmol/µL)	0.5 µL
dNTP mix (2.5 mM each)	1.0 µL
10X buffer	2.5 µL
$MgCl_2$	2.5 µL
Taq enzyme (3 U/µL)	0.5 µL
Water	13.5 µL
Total reaction volume	25.0 µL

TABLE 3. PCR cycle condition.

Temperature	94°C	95°C	61.5°C	72°C	72°C
Time	5 min	30 sec	40 sec	30 sec	10 min
Cycles		40 cycle			

The patients with at least three criteria were acquired for lab measurement including the subjects:obesity, fasting blood glucose, the level of LDL (low-density lipoprotein) and HDL (high-density lipoprotein). The thesis code is 15930503952005.

Extraction of genomic DNA and doing PCR

Genomic DNA of 200 samples above were isolated from 100 CC of blood with extracted ones using a standard kit GENET Bio. In order to make sure ourselves that DNA has the high quality, extracted DNA was placed on 1.5% Agarose gel. The concentration of DNA genomic was calculated, and it is ready for doing PCR[25].

Three ARMS-PCR Process

One pair of primer forward and one primer of reverse were designed on the partial fragment of CD38 gene based on rs: 6449181;

Forward1: GGCCCATCAGTTCACACAGGTCCAGC
Forward2: GGCCCATCAGTTCACACAGGTCCAGt
Reverse: AAATGCCAGCTCCCCTTCCCC

Note: Primers after designing were alignment with NCBI Network system (BLAST) and confirmed accuracy current primers with CD38 gene based rs6449181.

According to above primers, PCR program and its reaction were applied for getting sharp band on the gel electrophoresis as TABLE 2. PCR cycle condition is summarized in TABLE 3. PCR products were running on 1.5 percent gel electrophoresis to determine the quantity and quality of PCR products.

Sequencing and Sequence Analysis of Fragment of CD38 Gene

For accuracy of amplification of CD38 gene, it was sequenced and analyzed by Bioedit software version of 5.0.

Statistical analysis

Data were analyzed by SPSS software (version 20) using one-way analysis of variance. The Tukey post hoc test was used at the significant level of $P<0.05$.

RESULTS

Hormonal analysis

TABLE 4 revealed that hormonal and biochemical analysis can be considered as the means ±SD, and Tuckey's post hoc test. One-way ANOVA calculated the correlation between clinical characterizations and four groups (control, diabetics, cancer and cancer& diabetics). Due to the comparison between control,

TABLE 4. Mean value of anthropometric, metabolic program and heritability of control, diabetics, cancer-diabetic population.

Source	Normal (n=50)	Diabetic (n=25)	Cancer (n=25)	Cancer-diabetic (n=25)	Statistical significance
Age (years)	25–80	25–80	25–80	25–80	0.076^{NS}
Body mass index	26.23±3.32	31.56±2.32 30.50±2.80 31.50±2.82			$P<0.05$
Fasting insulin (µUI/mL)	10.88±2.43	14.65±2.34	14.61±2.20	15.61±2.30	$P<0.001$
Fasting blood glucose (mg/dL)	92.32±6.55	178.32±9.80	170.45±10.30	171.42±10.30	$P<0.001$
Heritability	Non	55%	57%	57%	0.092^{NS}
HDL-C (mg/dL)	60.65±8.1	54.34±5.45	52.55±4.50	52.34±4.50	$P<0.001$
LDL-C (mg/dL)	100.65±10.1	165.34±10.45	166.50±1.06	166.30±1.06	NS

HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; NS: not significant.

diabetics, cancer and the cancer with diabetes, it shows the high BMI, HDL cholesterol, fasting insulin and fasting blood glucose with significant index, along with the lower LDL cholesterol with insignificant index.

Clinical records of the control and patient groups including gender, heritability and history hyperglycaemia is shown in TABLE 5. By right of, nine samples were randomly selected to study the clinical records. The results show that the most cases have had the history of the inheritance diseases in family along with the history of diabetics and intestinal cancer diseases in family. FIGURE 1 shows that the status of distribution of the intestinal cancer in cases. Because of it, the range of incidence was 40 to 80 years old, and threshold of incidence was 70–80 years old.

TABLE 5. Clinical records of the control and patient groups including gender, heritability and history hyperglycaemia in patients is shown.

Sex	The history of inheritance diseases in family	The history of diabetics and intestinal cancer diseases in family	Hyper glycemic
Male	No	Yes	Yes
Male	Heart diseases	No	No
Male	No	Diabetics-cancer (his sister)	Yes
Female	Diabetic-Hepatic	Diabetics (her brother)	Yes
Female	No	No	Yes
Male	No	No	No
Female	No	No	Yes
Female	No	Diabetics-cancer (her brother)	No
Female	No	Cancer only (her brother and sister)	Yes

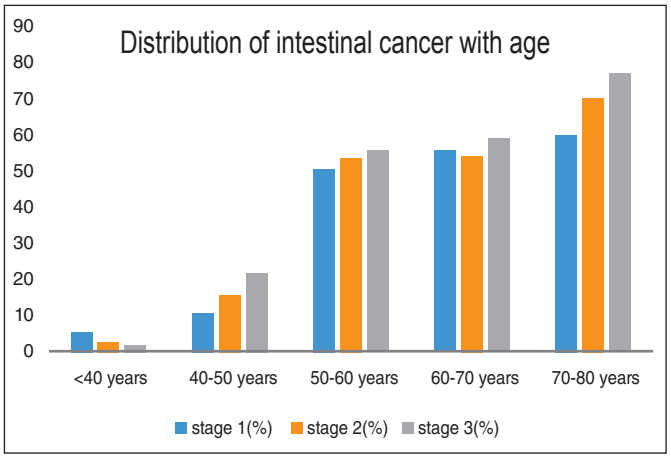


FIGURE 1. The distribution of the intestinal cancer related to the age showed that the most of cases belong to the range of 70–80 year old people.

FIGURE 2 shows that PCR product of CD38 gene is amplified by normal primer. The results show a 420bp fragment is related with the amplified rs6449181 of CD38 gene.

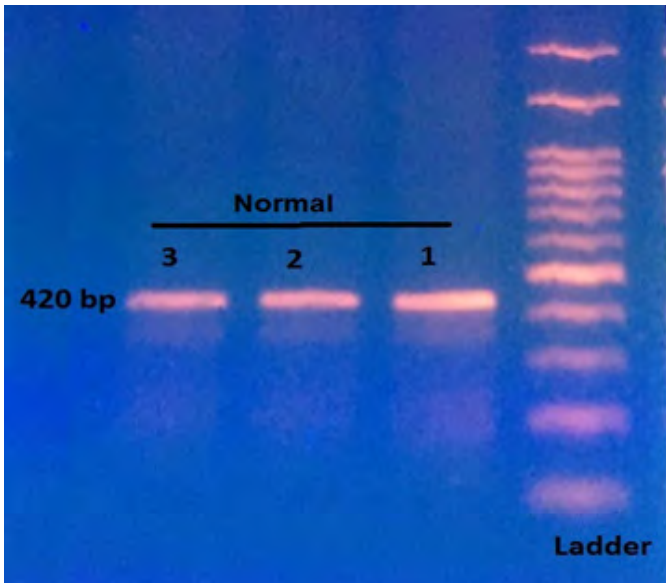


FIGURE 2. PCR product of rs6449181 of CD38 gene in normal group when used normal primer (F1) (lane 1, 2 and 3 and Ladder). The size of PCR product is sharp showing 420bp.

FIGURE 3 shows that PCR product of CD38 gene is amplified by mutant primer (lane 1, 3 and 4). Lane 2 is the control group, that is, the group without using primers of CD38 gene. The results show a sharp band in 420bp length is related with rs6449181. The results show a 420bp fragment related to rs6449181 of the amplified CD38 gene.

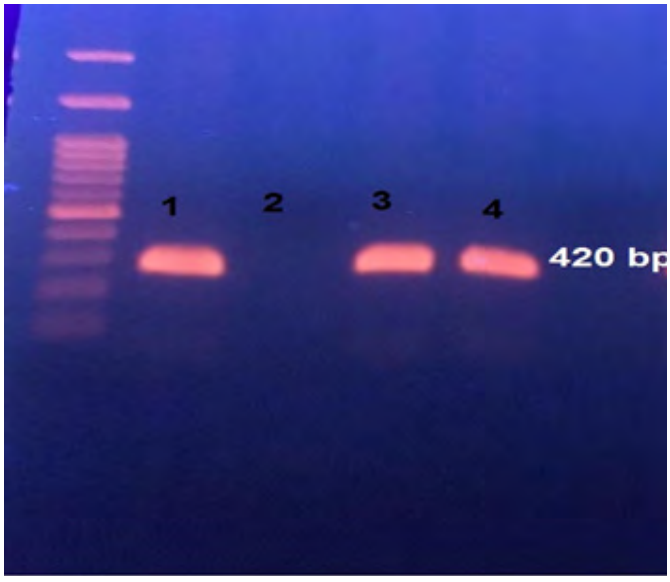


FIGURE 3. PCR product of rs6449181 of CD38 gene in cases group when used normal primer (F2) (lane 1, 3 and 4 is mutant and line of 2 is control group). The size of PCR product is sharp that was 420bp.

FIGURE 4 shows the alignment of the partial CD38 gene and CD38 gene in GenBank for verifying the results of three, amplification. The results show that both sequences have high homology, and they verified our PCR amplification. TABLE 6 shows the allelic and genotypic frequencies of CC, CT, and TT nucleotides of rs6449181: in CD38 gene in normal and cases group respectively. The frequencies of allelic and genotypic by Hardy-Weinberg equilibrium is insignificant between them (P value>0.05).

DISCUSSION

Today, various studies have shown that there is a link between diabetes and cancers in the gastrointestinal tract. Mellitus diabetes may increase the risk of many cancers, including breast, liver, pancreatic, colon, endometrium, kidney, and lymph and bladder cancer[26,27].

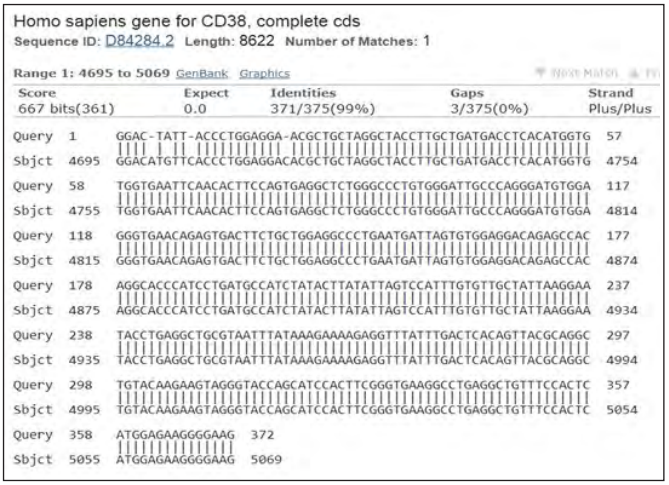


FIGURE 4. Results of BLAST analysis shows the relationship between partial CD38 gene (query) and CD38 gene in GenBank(Sbjct). According to our result between both sequences, the high homology is shown in the table, and it confirmed PCR product. TABLE 6. The allelic and genotypic frequencies of CC, CT, and TT nucleotides of rs:6449181 of CD38 gene in normal and patient samples, respectively.

In addition, most cancers are often related to diabetes and cancers. Insulin resistance reduced fat control, oxidative stress, and changes in the immune system. One of the most important gastrointestinal cancers is the gastric cancer, which is associated with age in men and most people[28,29].

Obesity, smoking, salt intake, and infection with helicobacter pylori and risk factors associated with gastrointestinal cancers. In addition, gastrointestinal cancers, especially gastric cancer, are abundant in developing countries such as the Middle East, South America. While it is low in North America and some parts of Africa[30,31].

The aim of this study is to evaluate the relationship between diabetes and one of the digestive cancers, such as intestinal cancer, based on the part of the CD38 gene in Iran.

The results of FIGURES 2, 3 and 4 shows that there is a relationship between mutations in rs: 6449181 of the CD38 gene with intestinal cancer by help of the ARMS-PCR technique.

In this study, 100 controls and 100 patients were used. The patient group was divided into three groups: first, diabetes, second, cancer and third, diabetic intestinal cancer.

Our results in both groups showed that mutation is in position rs: 6449181 of CD38 gene. Moreover, our results were evaluated with the results of Chin and Farn, 2014 between the diabetic and gastric cancer population. The population related to the age increasing with gastric cancer, most of the ones who were over the age of 30 and suffering from type 1 diabetes[32].

In addition, in Asian countries with type 2 diabetes, gastrointestinal cancers were examined, and then significant relationships were observed. Furthermore, Chin and Farn, 2014 were compared with control group from 17 cases including 6 patients and 11 healthy people with gastric cancer disease and diabetes. In this study, only the number of people who died has been investigated and there is a significant relationship. There was also a significant relationship between the prevalence of diabetes and gastrointestinal cancers with sex, age, obesity, smoking, salt intake, and infection with H.pylori[32]. These factors vary among different populations. In generally CD38 is a multi-functional transmembrane protein that was originally identified as a cell surface receptor and marker of lymphocyte differentiation and maturity. CD38 is also a major cellular NADase that can catalyze the synthesis of a series

TABLE 6. The allelic and genotypic frequencies of CC, CT, and TT nucleotides of rs:6449181 of CD38 gene in normal and patient samples, respectively. The results showed hardy Weinberg equilibrium that insignificantly between genotypic and allelic of rs:6449181.

rs:6449181	Genotype	N (n=200)	Frequency (%)	Expected genotype frequency under HWE	Allele	Allele frequency (%)	HWE (P-value)
	CC	10	9.5	9.10	C	66.1	0.24*
Normal	CT	48	50	50.00	T	33.9	
	TT	22	40.5	41.31			
	CC	44	17	16.21	C	31.67	0.21*
Cases	CT	28	30	27.23	T	68.23	
	TT	8	53	54.23			

HWE: Halfway wicket value. *Non-significant variation.

of second messengers, including cyclic ADPribose (cADPR) and nicotinic acid adenine dinucleotide phosphate (NAADP)[33]. At least three CD38 SNPs have been reported previously, and they were used to perform genotype-phenotype correlation studies. Abramenko et al., 2012 reported that rs6449182, a common SNP in intron 1 which was not included in their amplicons for that intron; a relatively uncommon nonsynonymous SNP, rs1800561, in exon 3 that results in an Arg140Trp change in encoded amino acid that they did not observe in their samples. rs1130169 of CD38 gene revealed that significantly associated with basal mRNA expression[34]. Although our studies are not similar, rs6449181 used here for the association between diabetic and intestinal cancer. However, we could find a relationship between them. In fact, there is a significant level of relationship between diabetic and intestinal cancer. TABLE 4 shows the regarding family inheritance. Most of the patients, who were studied, had a history of diabetes or heart disease. That is, there is a relationship between heart disease and diabetes in the present study. In addition, Scirica et al. 2013 reported that there is a relationship between a diabetes risk and the cardiovascular diseases. In fact, they suggested that there is a relationship between type 2 diabetes with the reduced incidence of two major aneurismal diseases, abdominal aortic aneurysm and subarachnoid hemorrhage[35]. Moreover, there are some relationships between increasing of blood glucose levels and heart disease. In addition, high blood glucose and high cholesterol have been observed in 90% of the heart patients. TABLE 5 shows patients' clinical parameters such as weight, fasting insulin, HDL and LDL cholesterol in normal and cases group. As we follow the diabetes and diabetic cancer, the level of blood glucoses, fasting insulin and LDL was higher than normal group. That is, the meta genomic can be cause of diseases. Moreover, sexicity is important for studies in current research. Most of population was women that apparently sexicity is engaged to relation between diabetics and cardiovascular diseases. However, aging is important for incidence of both diabetes and cancer. Beside there are some relationships between high Body mass index and risk of CRC. The prior report suggests that becoming overweight/ obese in early adulthood might affect the incidence of CRC and that body weight gain over the adult lifespan is associated with a slightly elevated CRC risk. These findings offer a significant strategy to aid the primary prevention of CRC in subjects with a high BMI starting at early adulthood[36].

The current research shows that most of them are about 40, and the threshold of the incidence belong to the patients who are 70–80 years. Meta-analysis also shows the relative risks for patients with the coronary heart disease is 2·63 for women and 1·85 for men who have diabetes. Sex difference in relation with type 2 diabetes, with outcomes other than coronary heart disease, has less been reported with conflicting results for stroke. The participants who are younger than 60-year-old people are, we noted the weak evidence of a slightly stronger association of type 2 diabetes with myocardial infarction. The women, in comparison with men, are more consistent with previous reports. However, we saw no other sex differences in associations between type 2 diabetes and cardiovascular outcomes.

TABLE 6 shows the frequency of allele and genotype and the frequency of heterozygosity in normal and case group, it is higher than homozygosity alleles, which increased the risk of incidence in healthy populations. Hardy Weinberg equilibrium was also investigated, and he could be no significant effect between the frequency of the allele and the number of subjects studied. Apparently, the use of larger populations could cause a change in this situation, since most researchers from large populations have more than 200 samples and have a meaningful effect; however, this parameter cannot be 100% verified. Larsson found that there was an increased risk of small intestine cancers (2.1 to 3.1 times) among diabetic patients who suffered from obesity for 4 years or more. The relationship between the incidence of obesity and the increased risk of cancer indicated the long-term effect of insulin on the risk of developing cancer[37].

The risk of developing intestine cancers increased with the duration of obesity and type 2 diabetes. Stattin et al., 2004, also found that the age will could have a significant role in the development of cancer and its relation with diabetes. In this regard, people aged 50 to 60 years were about 21.8% more likely than others to have cancer and diabetes were[38]. The impact of sex is also important in the development of cancer and diabetes, some cancers are more common in women, such as breast, uterine, and in men, prostate cancer, while men are more susceptible to diabetes than women[39]. Finally, we can conclude that CD38 gene has a relationship with type 2 diabetics that associated with intestinal cancer. Our aim in this sturvey is to study the situation of association between diabetic and cancer based CD38 gene. The functional this gene is autoimmune which is related with several human cancers. In the present study, we analyze and observe the significant effect of mutation on the part of the CD38 gene, which is rs:6449181, and besides it's associated with cancer and diabetes.

The subjects were often over 40 years old and were collected from the Mazandaran Province. ARMS-PCR results indicate the evaluated mutation for both patients and healthy subjects. FIGURE 4 shows that sequences of partial fragment of CD38 gene while alignment is with BLAST program. However, that is not position of rs: 6449181, it is confirmed both the partial CD38 gene and PCR amplification. Finally, we concluded that there is a relationship between intestinal cancer and diabetic syndrome based on rs: 6449181 of CD38 gene. Moreover, our result showed that the rate of incidence in heterozygote allelic is more than homozygote population. Hence, we should study more population in Iran.

Authors' contribution

Shokrzadeh M: study design and management.Rezaei A: study design and management. Goleij P and Salehabadi Y: perform tests. Ghassemi-Barghi N: statistical analyses. Behravan E: writing article, all authors read and approve final manuscript.

Orcid

Mohammad Shokrzadeh: 0000-0002-0071-6530.
Nasrin Ghassemi-Barghi: 0000-0002-0673-4262.
Abdolhasan Rezaei: 0000-0001-5062-5832.
Pouya Goleij: 0000-0002-2213-497X.
Elmira Behravan: 0000-0001-5532-6399.
Yaser Salehabadi: 0000-0002-9894-2076.

Shokrzadeh M, Goleij P, Behravan E, Ghassemi-Barghi N, Salehabadi Y, Rezaei A. Associação entre diabéticos e câncer intestinal com o risco de mutação no gene CD38 na população iraniana. Arq Gastroenterol. 2020;57(2):144-9.

RESUMO – **Contexto** – O câncer intestinal ocorre frequentemente em pacientes diabéticos tipo 2. O conceito que aumento dos níveis de insulina e fator de crescimento semelhante à insulina no sangue com diabetes tipo 2 sejam estimulados com o crescimento e esgotamento das paredes celulares clonadas, e a continuação desse processo levaria à deformação celular. Esta é a evidência para câncer intestinal em diabetes tipo 2 na população. **Objetivo** – Neste estudo, buscou-se descobrir a relação entre diabéticos e câncer intestinal com base na mutação genética CD38. **Métodos** – Foram coletadas amostras de duzentos habitantes, incluindo os normais e os casos. Produtos PCR relacionados ao rs 6449181do gene CD38 foi amplificado com a técnica ARMS-PCR, e uma banda afiada de 420 bp também foi observada. De acordo com três técnicas ARMS-PCR, três *primers* foram projetados pelo software Oligo7. Os *primers* incluem F1, F2 e R (amplificando para *primer* normal, mutante e reverso, respectivamente). **Resultados** – Esta banda foi observada usando um *primer* F1 que carrega o nucleotídeo do tipo selvagem usando um *primer* e quando é usado com o *primer* F2, ele traz o *primer* mutante para populações de pacientes com diabetes e diabetes-câncer. Além disso, foram analisados os resultados clínicos, incluindo índice de massa corporal, glicemia e nível de insulina. As médias ±SD e *Tuckey's post hoc test* foram significativas entre os parâmetros de caracterização clínica entre os casos e populações saudáveis. Foram avaliadas as frequências genéticas alélicas e o equilíbrio de Hardy-Weinberg entre nucleotídeos e observou-se o nível significativo entre os alelos e as frequências genéticas. **Conclusão** – Em geral, o presente estudo constatou que há relação entre diabetes e câncer intestinal entre as populações estudadas.

DESCRITORES – Diabetes mellitus tipo 2. Neoplasias intestinais. Genótipo. Polimorfismo genético.

REFERENCES

1. Zhang P-H, Chen Z-W, Lv D, Xu Y-Y, Gu W-L, Zhang X-H, et al. Increased risk of cancer in patients with type 2 diabetes mellitus: a retrospective cohort study in China. BMC Public Health. 2012;12:567.
2. Ren X, Zhang X, Gu W, Chen K, Le Y, Lai M, et al. Type 2 diabetes mellitus associated with increased risk for colorectal cancer: evidence from an international ecological study and population-based risk analysis in China. Public Health. 2009;123:540-4.
3. Szablewski L. Diabetes mellitus: influences on cancer risk.Diabetes Metab Res Rev. 2014;30:543-53.
4. Hassani M, Ghassemi-Barghi N, Modanloo M, Mohammadpour A, Shokrzadeh M. Cytotoxic effects of duloxetine on MKN45 and NIH3T3 cell lines and genotoxic effects on human peripheral blood lymphocytes. Arq Gastroenterol. 2019;56:372-6.
5. Braun S, Bitton-Worms K, LeRoith D. The link between the metabolic syndrome and cancer.Int J Biol Sci. 2011;7:1003.
6. Ansari M, Shokrzadeh M, Karima S, Rajaei S, Fallah M, Ghassemi-Barghi N, et al. New thiazole-2 (3H)-thiones containing 4-(3, 4, 5-trimethoxyphenyl) moiety as anticancer agents. Eur J Med Chem. 2020;185:111784.
7. Beam HA, Russell Parsons J, Lin SS. The effects of blood glucose control upon fracture healing in the BB Wistar rat with diabetes mellitus. J Orthop Res. 2002;20:1210-6.
8. Clemmons DR, Busby Jr WH, Brewer MT, Eisenberg SP, Thompson RC. Method for potentiating and inhibiting insulin-like growth factor activity. Google Patents; 1999.
9. Mohammadi H, Ghassemi-Barghi N, Malakshah O, Ashari S. Pyrethroid exposure and neurotoxicity: a mechanistic approach. Arh Hig Rada Toksikol. 2019; 70:74-89.
10. Giovannucci E, Harlan DM, Archer MC, Bergenstal RM, Gapstur SM, Habel LA, et al. Diabetes and cancer: a consensus report. CA Cancer J Clin. 2010;60:207-21.
11. Wang L-F, Huang C-C, Xiao Y-F, Guan X-H, Wang X-N, Cao Q, et al. CD38 deficiency protects heart from high fat diet-induced oxidative stress via activating Sirt3/FOXO3 pathway. Cell Physiol Biochem. 2018;48:2350-63.
12. Ghassemi-Barghi N, Varshosaz J, Etebari M, Dehkordi AJ. Role of recombinant human erythropoietin loading chitosan-tripolyphosphate nanoparticles in busulfan-induced genotoxicity: Analysis of DNA fragmentation via comet assay in cultured HepG2 cells. Toxicol in Vitro. 2016;36:46-52.
13. Ghassemi-Barghi N, Etebari M, Jafarian-Dehkordi A. Protective effect of amifostine on busulfan induced DNA damage in human hepatoma cells. Toxicol Mech Methods. 2017;27:52-7.
14. Kröber A, Seiler T, Benner A, Bullinger L, Brückle E, Lichter P, et al. VH mutation status, CD38 expression level, genomic aberrations, and survival in chronic lymphocytic leukemia. Blood. 2002;100:1410-6.
15. Antonelli A, Tuomi T, Nannipieri M, Fallahi P, Nesti C, Okamoto H, et al. Autoimmunity to CD38 and GAD in type I and type II diabetes: CD38 and HLA genotypes and clinical phenotypes. Diabetologia. 2002;45:1298-306.
16. Lian-xiang C, Ben-sui N, Xiang-ping L. (Department of Endocrine of Baoan District Hospital, Shenzhen 518101, Guangdong, P. R. China). Study on the clinical diagnostic criteria of latent autoimmune diabetes in adults. China Tropical Medicine. 2005;3. Available from: http://en.cnki.com.cn/Article_en/CJFDTotal-RDYX200503014.htm
17. Shokrzadeh M, Ghassemi-Barghi N. Melatonin loading chitosan-tripolyphosphate nanoparticles: Application in attenuating etoposide-induced genotoxicity in HepG2 cells. Pharmacology. 2018;102:74-80.
18. Shokrzadeh M, Mohammadpour A, Modanloo M, Hassani M, Barghi NG, Niroomand P. Cytotoxic effects of aripiprazole on MKN45 and NIH3T3 cell lines and genotoxic effects on human peripheral blood lymphocytes. Arq Gastroenterol. 2019;56:155-9.
19. Shokrzadeh M, Mohammadpour A, Hoseini V, Abediankenari S, Ghassemi-Barghi N, Tabari YS. Serum cytokine of IL-2, IL-10 and IL-12 levels in patients with stomach adenocarcinoma. Arq Gastroenterol. 2018;55:385-9.
20. Meyerhardt JA, Catalano PJ, Haller DG, Mayer RJ, Macdonald JS, Benson III AB, et al. Impact of diabetes mellitus on outcomes in patients with colon cancer. J Clin Oncol. 2003;21:433-40.
21. Pascal LE, Vêncio RZ, Page LS, Liebeskind ES, Shadle CP, Troisch P, et al. Gene expression relationship between prostate cancer cells of Gleason 3, 4 and normal epithelial cells as revealed by cell type-specific transcriptomes. BMC cancer. 2009;9:452.
22. Govindarajan R, Ratnasinghe L, Simmons DL, Siegel ER, Midathada MV, Kim L, et al. Thiazolidinediones and the risk of lung, prostate, and colon cancer in patients with diabetes. J Clin Oncol. 2007;25:1476.
23. La Vecchia C, Negri E, Decarli A, Franceschi S. Diabetes mellitus and colorectal cancer risk. Biomarkers. 1997;6:1007-10.
24. Larsson SC, Orsini N, Wolk A. Diabetes mellitus and risk of colorectal cancer: a meta-analysis. J Natl Cancer Inst. 2005;97:1679-87.
25. Albertsen M, Karst SM, Ziegler AS, Kirkegaard RH, Nielsen PH. Back to basics–the influence of DNA extraction and primer choice on phylogenetic analysis of activated sludge communities. PloS one. 2015;10:e0132783.
26. Khaw K-T, Wareham N, Luben R, Bingham S, Oakes S, Welch A, et al. Glycated haemoglobin, diabetes, and mortality in men in Norfolk cohort of European Prospective Investigation of Cancer and Nutrition (EPIC-Norfolk). BMJ. 2001;322:15.
27. Miłek T, Forysiński K, Myrcha P, Ciostek P. Diabetes association of polyps and colon cancer. Pol Przegl Chir. 2019;91:9-12.
28. Khaw K-T, Wareham N, Bingham S, Luben R, Welch A, Day N. Association of hemoglobin A1c with cardiovascular disease and mortality in adults: the European prospective investigation into cancer in Norfolk. Ann Intern Med. 2004;141:413-20.
29. Dashti SG, Li WY, Buchanan DD, Clendenning M, Rosty C, Winship IM, et al. Type 2 diabetes mellitus, blood cholesterol, triglyceride and colorectal cancer risk in Lynch syndrome. Br J Cancer. 2019:1-8.

30. Ryder R. The potential risks of pancreatitis and pancreatic cancer with GLP-1-based therapies are far outweighed by the proven and potential (cardiovascular) benefits.Diabet Med. 2013;30:1148-55.
31. Shokrzadeh M, Mohammadpour A, Ghassemi-Barghi N, Hoseini V, Abediankenari S, Tabari YS. Metallothionein-2A (rs1610216&rs28366003) gene polymorphisms and the risk of stomach adenocarcinoma. Arq Gastroenterol. 2019;56:367-71.
32. Tseng CH, Tseng FH. Diabetes and gastric cancer: the potential links. World journal of gastroenterology: World J Gastroenterol. 2014;20:1701.
33. Camacho-Pereira J, Tarragó MG, Chini CC, Nin V, Escande C, Warner GM, et al. CD38 dictates age-related NAD decline and mitochondrial dysfunction through an SIRT3-dependent mechanism. Cell Metab. 2016;23:1127-39.
34. Abramenko V, Yurchyshyn V, Goode P, Kitiashvili I, Kosovichev A. Detection of small-scale granular structures in the quiet sun with the new solar telescope. The Astrophysical Journal Letters. 2012;756:L27. doi 10.1088/2041-8205/756/2/L27.
35. Scirica BM, Bhatt DL, Braunwald E, Steg PG, Davidson J, Hirshberg B, et al. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. N Engl J Med. 2013;369(14):1317-26.
36. Zheng R, Du M, Zhang B, Xin J, Chu H, Ni M, et al. Body mass index (BMI) trajectories and risk of colorectal cancer in the PLCO cohort. Br J Cancer. 2018;119:130.
37. Organization WH. Obesity: preventing and managing the global epidemic: World Health Organization; 2000.
38. Stattin P, Lukanova A, Biessy C, Söderberg S, Palmqvist R, Kaaks R, et al. Obesity and colon cancer: does leptin provide a link? Int J Cancer. 2004;109:149-52.
39. Murthy VH, Krumholz HM, Gross CP. Participation in cancer clinical trials: race-, sex-, and age-based disparities. Jama. 2004;291:2720-6.

ORIGINAL ARTICLE

AG-2019-154
doi.org/10.1590/S0004-2803.202000000-26

Patterns of fiber intake among Brazilian adults: perceptions from an online nationwide survey

Maria do Carmo F **PASSOS**[1], Maira Libertad Soligo **TAKEMOTO**[2] and Luciana S **GUEDES**[3]

Received: 15 October 2019
Accepted: 9 January 2020

ABSTRACT – **Background** – Adequate fiber intake is associated with digestive health and reduced risk of several noncommunicable diseases and is recognized as essential for human health (World Health Organization, 2003). The World Health Organization (WHO) recommends a daily fiber consumption of ≥25 g, but previous studies observed a fiber intake in Brazil lower than recommended. **Objective** – We aimed to describe fiber intake among adults in Brazil and also respondents' knowledge and perceptions about their fiber intake. **Methods** – National online survey with community-dwelling Brazilian individuals. The survey was conducted during September 2018, using an online platform with closed-ended questions. A representative sample of Brazilian internet users stratified by sex, age, socioeconomic status and geographic region was adopted. Sample size was calculated using a 2% error margin and 95% confidence interval (n=2,000). Data was descriptively analyzed using measures of frequency, central tendency and dispersion. **Results** – Sample included 2,000 individuals who were well-balanced in terms of sex (51.2% female), with mean age of 35.9 years (most represented age group was 35–54 years, 39.6%) and from all country geographic regions (49.4% from Southeast). A total of 69.7% of them consider their usual diet as healthy and 78.4% reported consuming fibers regularly. Fibers from natural sources are consumed at least once a day by 69.5% of the sample, while daily fiber supplements were reported by 29.9%. Absence of regular fiber intake was reported by 21.7% of respondents and the most common reason was "lack of knowledge about fiber sources" (39.3%). When informed about the food sources of each type of fiber (soluble and insoluble) and asked about the regular intake, only 2.5% answered that they do not consume any of them regularly (as opposed to 21.7% before receiving information about specific fiber sources). **Conclusion** – Our findings indicate that fiber intake in Brazil is probably insufficient with a high proportion of individuals reporting irregular or absent ingestion of fiber sources in their daily lives. Lack of knowledge about fiber sources and fiber types seems to play a role in this inadequate intake, highlighting the need for nutritional education to achieve healthy dietary patterns in the country.

HEADINGS – Dietary fiber. Diet surveys. Socioeconomic factors. Health knowledge, attitudes, practice.

INTRODUCTION

Adequate fiber intake is associated with digestive health and reduced risk of several noncommunicable diseases, and is recognized as essential for human health[1-7]. In terms of gastrointestinal (GI) conditions, evidence has suggested that adequate fiber intake has also potential benefits in the management of chronic constipation and irritable bowel syndrome[8,9]. Additionally, two systematic reviews with meta-analyses observed that individuals with higher consumption of fibers had a lower mortality rate than those eating less fibers for both cardiovascular causes, cancer and all-cause mortality[10,11]. The physiological mechanism that explains the health benefits associated to dietary fibers is not completely understood, but local and systemic effects are expected once fiber intake is a risk factor for markedly diverse conditions[12].

Following the recognition of a global inadequate fiber intake, in 2003 the World Health Organization (WHO) and the Food and Agriculture Organization of the United Nations (FAO) recommended a daily fiber consumption of ≥25 g as a strategy to prevent noncommunicable diseases[13]. The Brazilian Ministry of Health adopted this recommendation as stated in the National Nutritional Guide for the Brazilian Population and also established a target intake of 5g per day for children[14,15].

Despite convincing evidence and explicit guidelines from official health agencies and institutions, previous studies have identified an inadequate fiber intake in the Brazilian population. Sardinha et al. 2014[16] assessed the fiber availability (grams per day) of Brazilian households using data from a national survey. Authors stated that the general household availability was insufficient (ranging from 9.9 to 21.4 grams per day) and that lower income and rural households presented higher availability than higher income and urban ones. Mattos et al. 2015[17] identified a higher mean daily intake of 24 g (17 g insoluble and 7 g soluble), with higher means for men (29 g) than women (20 g). Santos et al. 2016[18] observed a low proportion of individuals meeting the adequate intake (2.0%) and an average daily intake of 13.1 g.

At the same time, previous reports showed that individuals' knowledge about dietary patterns and fiber role in diet are associated with increased fiber intake[19-21]. Thus, the present study was designed to describe fiber intake patterns among adults in Brazil and also respondents' knowledge and perceptions about their fiber intake, through a nationwide web-based survey.

Declared conflict of interest of all authors: Passos MCF: Global Advisory Board Member for Takeda, Speaker for EMS, Aché, Mantecorp. Takemoto MLS: Consultant Epidemiologist for Takeda, Abbvie, Astrazeneca, Biogen, and Novartis. Guedes LS: Sr Medical Manager for Gastroenterology at Takeda.
Disclosure of funding: the study was supported by Takeda Pharmaceuticals Brazil.
[1] Universidade Federal de Minas Gerais, Faculdade de Medicina, Belo Horizonte, MG, Brasil. [2] ANOVA Consultoria em Saúde, Rio de Janeiro, RJ, Brasil. [3] Takeda Pharmaceuticals Brazil, São Paulo, SP, Brasil
Corresponding author: Luciana S Guedes. E-mail: luciana.guedes@takeda.com

METHODS

We performed a cross-sectional analysis of data from a national web-based survey that aimed to describe patters of fiber intake in community-dwelling Brazilian individuals. The survey was conducted from September 14th to 28th, 2018. To recruit a representative sample of Brazilian internet users who were 16 years of age or older, quotas for sex, age, socio-economic status, and geographic region were used. After receiving information about study procedures and agreeing in participating, respondents were presented with questions about demographics and socioeconomic status (using the Brazilian Criteria for Socio-Economic Classification)[22]. Fiber intake was self-reported using the following questions: (i) Do you consume fibers in your daily life?; (ii) If yes, with which frequency do you usually consume each source of fibers (natural and supplements)?; (iii) If not, what are the reasons for not consuming?. Additionally, individuals were presented with lists of fiber sources to answer about their usual intake and also about nutritional knowledge, intestinal function and GI symptoms. Thus, our primary outcome was the pattern of fiber intake in terms of consumption prevalence and frequency.

This study was based on results of an opinion survey and, thus, no approval was required from the Research Ethics Committee. Likewise, it was not necessary to sign an Informed Consent Form. However, all procedures performed are governed by ethical standards of the Brazilian Association of Research Companies (ABEP) and of the European Society of Market Research (ESOMAR), in compliance with the International Standard for Quality on Market and Opinion Research – ISO 20252:2006 and the International Standard for Quality Management ISO 9001:2000.

Statistical analyses

A descriptive approach was adopted using measures of frequency, central tendency and dispersion, thus hypothesis tests or other exploratory methods were not planned. As a descriptive study, hypothesis tests and models were not used in the present analysis. Sample size was calculated using a 2% error margin and 95% confidence interval (n=2,000).

RESULTS

The final sample was comprised of 2,000 individuals, 51.2% females, with an average of 36 years old. Socio-demographic sample characteristics are presented in TABLE 1.

In terms of fiber intake (TABLE 2), 78.4% of respondents reported consuming fibers regularly. This proportion was similar for most age groups, with the exception of 55 or more years (86.0%). A similar pattern was observed for both male and female respondents. The self-reported usual fiber intake ranged from 75.3% in the South region to 83.6% in the North region. The absolute difference in the percentage of individuals reporting fiber intake between the lower (C) and higher (A) income groups was 7.2% (75.9% and 93.1%, respectively).

As observed in TABLE 3, the frequency of individuals reporting absence of fiber intake varied depending on the assessment method. While 21.7% of respondents informed that they usually do not consume fibers when questioned without any additional information about fiber sources or foods, the frequency markedly decreased when specific foods and sources where mentioned. When presented with a list of foods that are considered fiber sources, individuals

TABLE 1. Sample characteristics.

Characteristics	N	%
Age		
16–24 years	446	22.3
25–34 years	548	27.4
35–54 years	792	39.6
55+	214	10.7
[Mean ±SD]	35.9±12.7	
Sex		
Male	976	48.8
Female	1024	51.2
Geographic region		
North	110	5.5
Northeast	399	20.0
Midwest	175	8.8
Southeast	988	49.4
South	328	16.4
Brazilian Criteria for Socio-Economic Classification		
Class A	58	2.9
Class B	662	33.1
Class C	1280	64.0

SD: standard deviation.

TABLE 2. Self-reported consumption of fibers by demographic characteristics.

Characteristics	Fiber intake*	
	N	%
Total sample (n=2,000)	1.567	78.4
Age		
16–24 years (n=446)	347	77.8
25–34 years (n=548)	430	78.5
35–54 years (n=792)	606	76.5
55+ (n=214)	184	86.0
Sex		
Male (n=976)	760	77.9
Female (n=1024)	807	78.8
Geographic region		
North (n=110)	92	83.6
Northeast (n=399)	320	80.2
Midwest (n=175)	137	78.3
Southeast (n=988)	771	78.0
South (n=328)	247	75.3
Brazilian Criteria for Socio-Economic Classification		
A (n=58)	54	93.1
B (n=662)	541	81.7
C (n=1280)	972	75.9

*Respondents who answered Yes for the question "Do you consume fibers in your daily life?".

TABLE 3. Self-reported lack of consumption of fibers using different assessment methods.

Characteristics	N	%
Answer to the question "Do you consume fibers in your daily life?" (No)	433	21.7
Answer to the question "Considering the following list of foods, what is your frequency of consumption?" (Never)		
Nuts and Seeds	358	17.9
Whole Grains	75	3.8
Legumes	24	1.2
Vegetables and greens	18	0.9
Fruits	12	0.6
Answer to the question "Considering the two types of fibers (soluble and insoluble) and their listed sources, what type are you able to ingest in your daily life?"*		
Soluble fibers	821	41.1
Insoluble fibers	235	11.8
Both types	895	44.8
None	49	2.5

*Respondents were presented with a list of fibers sources of each type before answering as following: soluble fibers such as fruit pulp, vegetables and legumes; insoluble fibers such as whole grains and fruit peels.

answering that they never consume each specific item ranged from 0.6% (fruits) to 17.9% (nuts and seeds). In a similar manner, when fibers were presented segmented by soluble and insoluble forms with a list of sources of each type, the frequency of individuals answering that they do not consume any of them was 2.5%.

Among 433 respondents who answered that they do not consume fibers in their usual life, the most frequent reasons for the absence of fiber intake were "Lack of knowledge about fiber sources" (39.3%) and "The costs would be high" (29.6%), as shown in FIGURE 1.

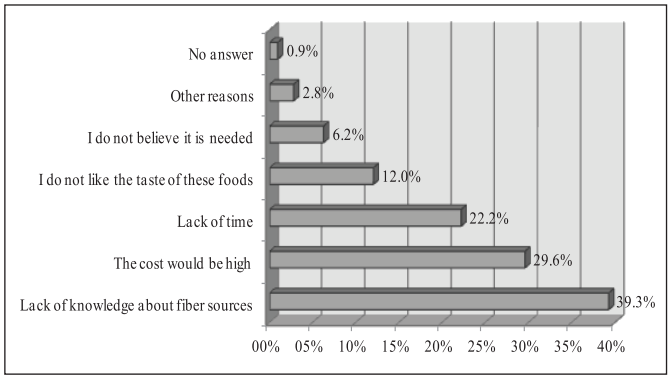


FIGURE 1. Reasons for the absence of fiber consumption (n=433).

TABLE 4 presents the frequency of fiber daily consumption (at least once a day) according to type of source (natural, as presented in foods or fiber supplements) and demographic characteristics. In the total sample, 69.5 and 29.9% of individuals reported daily consumption of natural sources and fiber supplements, respectively. In numeric terms, natural sources were more frequently reported by those with 55 or more years (78.3%), residents in the South region (74.5%), and part of the higher income group (A, 83.3%). Fiber supplements however were less frequent in the 55+ age group and in the A income group. The lower intake of natural sources was observed for the North region (57.6%), while fiber supplements were less frequent in the Midwest region. Male and female individuals presented similar pattern of fiber source intake.

TABLE 4. Self-reported daily consumption of natural fibers and fiber supplements by demographic characteristics.

Characteristics	Daily intake of natural sources of fiber		Daily intake of fiber supplements	
	N	%	N	%
Total sample* (n=1,567)	1,089	69.5	469	29.9
Age				
16–24 years (n=446)	230	66.3	111	32.0
25–34 years (n=548)	290	67.4	134	31.2
35–54 years (n=792)	425	70.1	186	30.7
55+ (n=214)	144	78.3	38	20.7
Sex				
Male (n=976)	534	66.2	226	29.7
Female (n=1,024)	555	68.8	243	30.1
Geographic region				
North (n=110)	53	57.6	22	23.9
Northeast (n=399)	228	71.3	115	35.9
Midwest (n=175)	85	62.0	29	21.2
Southeast (n=988)	539	69.9	229	29.7
South (n=328)	184	74.5	74	30.0
Brazilian Criteria for Socio-Economic Classification				
A (n=58)	45	83.3	14	25.9
B (n=662)	402	74.3	172	31.8
C (n=1,280)	642	66.0	283	29.1

*Among those respondents who answered yes for the question "Do you consume fibers in your daily life?"

Respondents also answered questions assessing their knowledge about fiber intake, diet and intestinal function, as shown in TABLE 5. In the total sample, 69.7% considered their diet as healthy and 79.2% classified their intestinal function as regular. 74.2% and 30.0% reported that they recognize the role of fiber in regulate intestinal function and the difference between soluble and insoluble fibers, respectively. Gastrointestinal symptoms most frequently informed by subjects with self-reported irregular function were constipation, abdominal bloating and flatulence (TABLE 5). Self-reported frequency of evacuation was at least once a day for 76.0% of individuals.

TABLE 5. Self-perception and knowledge about fiber intake, diet and intestinal function aspects.

Characteristics	N	%
Rated diet as healthy	1,394	69.7
Rated intestinal function as regular	1,584	79.2
Affirmed to recognize the role of fibers in the intestinal function	1,484	74.2
Affirmed to recognize the difference between soluble and insoluble fibers	599	30.0%
GI symptoms among those with self-reported irregular intestinal function (n=416)		
Constipation	318	76.4
Abdominal bloating	281	67.5
Flatulence	269	64.7
Abdominal pain	250	60.1
Diarrhea	104	25.0
Hemorrhoids	1	0.2
No answer	3	0.7
Self-reported frequency of evacuation (total sample)		
>1/day	548	27.4
Daily	972	48.6
5 times/week	183	9.2
3 times/week	167	8.4
2 times/week	84	4.2
Weekly	46	2.3

DISCUSSION

The study enrolled a large sample of Brazilian community-dwelling individuals and assessed self-reported fiber intake patterns using a representative sample of Brazilian internet users, as evidenced by geographic distribution and demographic characteristics of the sample, particularly socio-economic status. Our findings indicate that fiber intake in Brazil is probably insufficient with a high proportion of individuals reporting irregular or absent ingestion of fiber sources in their daily lives. Previous studies with Brazilian samples used different methods and outcomes, impairing our ability to make comparisons[16-18]. Despite this fact, it is consistent across studies[16-18] that Brazilian individuals do not meet dietary fiber intake targets[13-15] or have low availability of fibers in their diet.

Fiber intake patterns were not homogeneous among socio-demographic subgroups, with higher frequency of any fiber intake among older individuals (over 55 years old), those living in the North and Northeast region and those with higher income. When fiber consumption was assessed according to the type of source (natural or supplements) among those reporting any fiber intake, daily consumption (at least once a day) of natural sources was also more common among those with higher age and higher income, but South region was the one with the highest proportion (and North region had the lowest value). In opposition, daily fiber supplements were less common among older (55+ years) respondents, those living in the North and Midwest region and with higher income. Male and female individuals presented a very similar pattern. It is important to highlight that this study adopted a descriptive approach and that statistical between-group differences were not tested, thus these observations take into account the numeric differences between individuals presenting each characteristic. As the sample size in our study is large, it is reasonable to believe that these differences are significant, but the observation for the high income group (A) is more prone to bias, due to its relatively small size.

Santos et al. 2016[18] also observed a positive effect of higher income and older age in the ingestion of fibers. In an opposite direction, Sardinha et al. 2014[16] observed higher fiber availability in lower income households and those located in the North and Northeast region. The national Family Budget Research conducted by the Brazilian Institute of Geography and Statistics in 2008-2009 assessed the fiber intake adequacy according to sex and age and observed the prevalence of insufficient fiber intake ranging from 60.0% among individuals aged ≥60 years to 82.0% among those with 10–13 years, without relevant differences between male and female individuals (very similar to our findings)[23]. As outcomes and exposure variables definitions were marked diverse among these studies and ours, it is difficult to establish comparisons, but it seems that the relationship among income and dietary fiber intake still needs comprehensive evaluation, while the interaction with age and sex seems more well-established in Brazilian reports.

Lack of knowledge about fiber sources and fiber types seems to play a significant role in the observed inadequate intake. Over 20% of the sample reported absence of fiber ingestion when fiber sources were not listed or mentioned. This percentage was meaningly reduced when lists of foods and fiber sources were explicitly presented and individuals were asked if they usually consume each item, probably indicating that the self-reported absence of fiber consumption is overestimated by individuals' inability to recognize fiber sources in their diet. This is reinforced by the high proportion of individuals affirming that they do not consume fibers because of lack of knowledge about fiber sources or due to financial constraints. Foods and ingredients that are widely available in Brazil and are not considered high-cost, as beans or cassava flour[16], are well-established fiber sources, but our findings may demonstrate that the general population do not see them as rich in fibers. Previous observational studies investigated the impact of individuals' dietary beliefs and nutrition knowledge in the dietary intake and clearly demonstrated an association between these factors[19-21].

In our sample, one in five individuals classified intestinal function as irregular, and a high proportion of those individuals presents significant gastrointestinal symptoms (constipation, abdominal bloating, and flatulence). Our data do not allow a more detailed estimation of constipation prevalence, once the presence of gastrointestinal symptoms was assessed only among those with self-rated irregular intestinal function (n=416). Nevertheless, at least 318 out of 2,000 respondents (15.9%) reported constipation in our sample and this is worth mentioning once fiber consumption is the first line strategy for constipation management in clinical guidelines[24]. It is reasonable to affirm that respondents in our sample recognize their constipation but have inadequate knowledge about how to manage this condition, once they do not identify fiber sources in their usual diet or do not ingest them regularly. Our study main limitation is the recall bias risk since fiber intake patterns were self-reported and respondents demonstrated a limited knowledge about fiber sources in their diet. Additionally, our study was not designed to assess adequate intake using objective measures (grams per day, for example)

or to collect data that would allow comparisons with widely accepted intake targets or with previously published reports on the topic. Despite these limitations, our survey enrolled a large national sample of individuals in the community setting, representative of Brazilian internet users, allowing an overview of fiber intake patterns in the country that seems consistent with previous studies. Future research could further investigate Brazilian individuals' beliefs, expectations and knowledge about dietary fiber intake and also to assess the effectiveness of nutritional education towards healthy diet.

CONCLUSION

Our findings indicate that fiber intake in Brazil is probably insufficient with a high proportion of individuals reporting irregular or absent ingestion of fiber sources in their daily lives. Lack of knowledge about fiber sources and fiber types seems to play a role in this inadequate intake, highlighting the need for nutritional education to achieve healthy dietary patterns in the country.

Authors' contribution

All authors contributed equally to conceptual planning of this analysis and interpretation of study findings; critically revised and modified the manuscript for relevant intellectual content; and approved the final version to be published. Takemoto MLS conducted data analysis and wrote the preliminary version of the manuscript.

Orcid

Maria do Carmo F Passos: 0000-0002-5247-9477.
Maira Libertad Soligo Takemoto: 0000-0002-7016-2879.
Luciana S Guedes: 0000-0002-8901-2600.

Passos MCF, Takemoto MLS, Guedes LS. O padrão de consumo de fibras entre adultos brasileiros: percepções de um inquérito nacional online. Arq Gastroenterol. 2020;57(2):144-9.

RESUMO – **Contexto** – A adequada ingestão de fibras está diretamente associada à saúde digestiva e é reconhecida como essencial à saúde humana (World Health Organization, 2003). A Organização Mundial da Saúde (OMS) recomenda consumo diário de fibras de ≥25 g, mas estudos prévios observaram uma ingesta de fibras no Brasil abaixo do recomendado. **Objetivo** – Descrever a ingestão, o conhecimento e as percepções sobre o consumo de fibras entre adultos brasileiros. **Métodos** – Inquérito nacional online com indivíduos brasileiros na comunidade. O inquérito foi conduzido em setembro de 2018, usando uma plataforma online com questões fechadas. Uma amostra representativa dos usuários de internet no Brasil estratificada por sexo, idade, status socioeconômico e região geográfica foi utilizada. O tamanho da amostra foi calculado usando uma margem de erro de 2,0% em um intervalo de confiança de 95% (n=2.000). Os dados foram analisados descritivamente usando medidas de frequência, tendência central e dispersão. **Resultados** – A amostra incluiu 2.000 indivíduos equilibrados em termos de sexo (51,2% mulheres), com idade média de 35,9 anos (faixa etária mais representada foi 35–54 anos, 39,6%) e de todas as regiões geográficas do país (49,4% do Sudeste). Dos respondentes, 69,7% consideram sua dieta usual como saudável e 78,4% relataram consumir fibras regularmente. Fibras de fontes naturais são consumidas pelo menos uma vez ao dia por 69,5% da amostra, enquanto que suplementos de fibras, por 29,9%. O não consumo regular de fibras foi relatado por 21,7% dos respondentes e a causa mais comum para tal foi "falta de conhecimento sobre fontes de fibras" (39,3%). Quando informados sobre fontes de fibra de cada tipo (solúvel e insolúvel) e interrogados sobre a ingestão regular, apenas 2,5% responderam não consumir nenhuma delas regularmente (por oposição a 21,7% antes de receberem informação sobre fontes específicas de fibras). **Conclusão** – Nossos achados indicam que a ingestão de fibras no Brasil é provavelmente insuficiente com uma alta proporção de indivíduos relatando consumo ausente ou irregular de fontes de fibras no cotidiano. Falta de conhecimento sobre fontes e tipos de fibras parece desempenhar um papel relevante nesta ingestão inadequada, reforçando a necessidade de educação nutricional para alcançar padrões alimentares saudáveis no país.

DESCRITORES – Fibras na dieta. Inquéritos sobre dietas. Fatores socioeconômicos. Conhecimentos, atitudes e prática em saúde.

REFERENCES

1. Threapleton DE, Greenwood DC, Evans CEL, Cleghorn CL, Nykjaer C, Woodhead C, et al. Dietary Fiber Intake and Risk of First Stroke. Stroke. 2013;44:1360-8.
2. Chiavaroli L, Mirrahimi A, Sievenpiper JL, Jenkins DJA, Darling PB. Dietary fiber effects in chronic kidney disease: a systematic review and meta-analysis of controlled feeding trials. Eur J Clin Nutr. 2015;69:761-8.
3. Chen J-P, Chen G-C, Wang X-P, Qin L, Bai Y. Dietary Fiber and Metabolic Syndrome: A Meta-Analysis and Review of Related Mechanisms. Nutrients. 2017;10:24.
4. McRae MP. Dietary Fiber Intake and Type 2 Diabetes Mellitus: An Umbrella Review of Meta-analyses. J Chiropr Med. 2018;17:44-53.
5. Chen K, Zhao Q, Li X, Zhao J, Li P, Lin S, et al. Dietary Fiber Intake and Endometrial Cancer Risk: A Systematic Review and Meta-Analysis. Nutrients. 2018;10:945.
6. McRae MP. The Benefits of Dietary Fiber Intake on Reducing the Risk of Cancer: An Umbrella Review of Meta-analyses. J Chiropr Med. 2018;17:90-6.
7. Ma Y, Hu M, Zhou L, Ling S, Li Y, Kong B, et al. Dietary fiber intake and risks of proximal and distal colon cancers. Medicine (Baltimore). 2018;97:e11678.
8. Shen L, Huang C, Lu X, Xu X, Jiang Z, Zhu C. Lower dietary fiber intake, but not total water consumption, is associated with constipation: a population-based analysis. J Hum Nutr Diet. 2019;32:422-31.
9. Moayyedi P, Quigley EMM, Lacy BE, Lembo AJ, Saito YA, Schiller LR, et al. The Effect of Fiber Supplementation on Irritable Bowel Syndrome: A Systematic Review and Meta-analysis. Am J Gastroenterol. 2014;109:1367-74.
10. Liu L, Wang S, Liu J. Fiber consumption and all-cause, cardiovascular, and cancer mortalities: A systematic review and meta-analysis of cohort studies. Mol Nutr Food Res. 2015;59:139-46.
11. Kim Y, Je Y. Dietary Fiber Intake and Total Mortality: A Meta-Analysis of Prospective Cohort Studies. Am J Epidemiol. 2014;180:565-73.
12. Mcrorie JW, Fahey GC. A review of gastrointestinal physiology and the mechanisms underlying the health benefits of dietary fiber: Matching an effective fiber with specific patient needs. Clin Nurs Stud. 2013;1:82-92.
13. World Health Organization, Food and Agriculture Organization of the United Nations. Diet, nutrition and the prevention of chronic diseases. Geneva; 2003.
14. Brasil. Ministério da Saúde. Guia alimentar para a população brasileira. Brasília; 2014.
15. Brasil. Ministério da Saúde. Dez passos para uma alimentação saudável: guia alimentar para crianças menores de dois anos Um guia para o profissional da saúde na atenção básica. Brasília; 2013.
16. Sardinha AN, Canella DS, Martins APB, Claro RM, Levy RB. Dietary sources of fiber intake in Brazil. Appetite. 2014;79:134-8.

17. De Mattos LL, Martins IS. Consumo de fibras alimentares em população adulta. Rev Saude Publica. 2000;34:50-5.
18. Santos PVF dos, Sales CH, Vieira DAS, de Mello Fontanelli M, Marchioni DM, Fisberg RM. Family income per capita, age, and smoking status are predictors of low fiber intake in residents of São Paulo, Brazil. Nutr Res. 2016;36:478-87.
19. Smith AM, Owen N. Associations of social status and health-related beliefs with dietary fat and fiber densities. Prev Med (Baltim). 1992;21:735-45.
20. Auld GW, Nitzke SA, McNulty J, Bock MA, Bruhn CM, Gabel K, et al. A Stage-of-Change Classification System Based on Actions and Beliefs regarding Dietary Fat and Fiber. Am J Heal Promot. 1998;12:192-201.
21. Królak M, Jeżewska-Zychowicz M, Sajdakowska M, Gębski J. Does Perception of Dietary Fiber Mediate the Impact of Nutrition Knowledge on Eating Fiber-Rich Bread? Nutrients. 2017;9:1255.
22. Associação Brasileira de Empresas de Pesquisa. Critério de Classificação Econômica Brasil 2015. ABEP; 2015 [Internet]. [cited 2019 Jun 18]. Available from: www.abep.org/Servicos/Download.aspx?id=09&p=cb
23. Instituto Brasileiro de Geografia e Estatítica (IBGE). Pesquisa de Orçamentos Familiares 2008-2009: Análise do Consumo Alimentar Pessoal no Brasil. Rio de Janeiro: IBGE; 2011. 150 p.
24. World Gastroenterology Organisation. World Gastroenterology Organisation Practice Guideline – Constipation. Milwaukee; 2010.

ORIGINAL ARTICLE

AG-2019-163
doi.org/10.1590/S0004-2803.202000000-28

Oral and pharyngeal transit in functional heartburn

Rachel Aguiar **CASSIANI** and Roberto Oliveira **DANTAS**

Received: 19 November 2019
Accepted: 17 January 2020

ABSTRACT – **Background** – Gastroesophageal reflux disease is associated with slower transit of the bolus through the pharynx and upper esophageal sphincter. Functional heartburn has similar symptoms to gastroesophageal reflux disease, however, the symptoms are not caused by reflux. **Objective** – The aim of this investigation was to evaluate oral and pharyngeal transit in patients with functional heartburn, with the hypothesis that, similar to patients with gastroesophageal reflux disease, they have changes in pharyngeal and upper esophageal sphincter transit time. **Methods** – Oral and pharyngeal transit was evaluated by videofluoroscopy in eight women with functional heartburn, five with mild dysphagia for solid foods, and 12 female controls. Controls and patients swallowed in duplicate 5 mL and 10 mL of liquid and paste boluses. **Results** – No difference in the oral or pharyngeal transit time was found between patients and controls. No aspiration of bolus into the airways was detected in any individual. Pharyngeal residues were detected in the same proportion of swallows, in patients (12.5%) and controls (15.0%), after swallows of 10 mL paste bolus. **Conclusion** – Oral, pharyngeal and upper esophageal sphincter transit time are similar in patients with functional heartburn to healthy controls.

HEADINGS – Heartburn. Deglutition. Upper esophageal sphincter. Gastroesophageal reflux.

INTRODUCTION

Heartburn may be caused by conditions such as erosive reflux disease (ERD), non-erosive reflux disease (NERD), hypersensitive esophagus (HE) and functional heartburn (FH). The diagnosis of each of these diseases is made by clinical manifestations, upper endoscopy and by esophageal 24-hour pH or pH/impedance monitoring[1]. FH is a functional esophageal disease characterized by heartburn, failure to respond to proton pump inhibitor therapy, normal esophageal endoscopy, normal 24 hours pH monitoring and a negative symptom-reflux association[1-4]. Although FH has similar symptoms to gastroesophageal reflux disease (GERD), it is not considered as consequence of gastroesophageal reflux, and is investigated by the same sequence of tests[1-5].

GERD is associated with changes in the pharyngeal phase of swallowing, with longer transit time through the pharynx and the upper esophageal sphincter[6,7]. It is possible that this slower transit time causes dysphagia, a common complaint in patients with GERD[7-10], mainly in those with esophagitis[7].

This investigation evaluated the oral and pharyngeal phases of liquid and paste swallow in patients with FH. The hypothesis was that, similar to GERD, FH is also associated with changes in the pharyngeal phase of swallowing.

METHODS

Videofluoroscopic evaluation of swallowing was performed in eight patients with FH and in 12 healthy controls.

Patients with FH had the symptom at least three times a week for more than six months, a normal endoscopic examination, normal esophageal manometric examination, a 24-hour esophageal pH monitoring (5 cm from the lower esophageal sphincter) showing a pH <4 below 4.2% of the time, and a negative symptom-reflux association. Six patients had cough and five had mild dysphagia for solid foods. Dysphagia was evaluated by the answer to the question "Do you have swallowing difficult". If the answer was "yes" they evaluated the intensity of dysphagia by the classification mild, moderate, severe, which reflect they own perception of the intensity of the problem, and if the difficult was for liquid and/or solid foods. All FH patients were women, aged 41±12 years, median 42 (25–56) years. They did not have any other esophageal or gastrointestinal disorders, or any cardiac, endocrinological or neurologic disease, and were in treatment with proton pump inhibitors without good response, in the outpatient clinic of the hospital. They were instructed to refrain from taking any medication for at least seven days before the esophageal motility testing, 24 hours pH monitoring, and the videofluoroscopic evaluation.

The control group consisted of 12 women, aged 53±15 years, median 54 (29–72) years. They were asymptomatic, did not have swallowing difficulties, or any gastrointestinal, cardiac, endocrinological or neurological disease and did not take medications. The study was approved by the Research Ethics Committee of the hospital (IRB 5703/2007) and all patients and volunteers gave written informed consent to participate in the investigation. None of the individuals included in the investigation had a drinking or smoking habit.

Manometry, pH-metry and videofluoroscopy were performed as previously described[7]. Manometry and pH-metry was performed in the patients with heartburn only. Manometry was performed with water-perfused system to evaluate the esophageal motility and identify the esophageal-gastric junction. The pH sensor was placed 5 cm proximal to the esophageal-gastric junction and a 24-hours esophageal pH monitoring was conducted.

Declared conflict of interest of all authors: none
Disclosure of funding: no funding received
Dantas RO is a member of the Board of Directors of the International Dysphagia Diet Standardisation Initiative (IDDSI), Brisbane, Australia.
Universidade de São Paulo, Faculdade de Medicina de Ribeirão Preto, Departamento de Clínica Médica, Ribeirão Preto, SP, Brasil.
Corresponding author: Roberto Oliveira Dantas. E-mail: rodantas@fmrp.usp.br

Videofluoroscopy was done with an Arcomax angiograph unit (Phillips, model BV 300, Veenpluis, The Netherlands). The images were recorded at 30 frames/second on the unit EDSR 100, v1.2 Everfocus (Taipei, Taiwan), and analyzed on the monitor DVR of the same manufacturer, with the digital clock of the apparatus indicating time in minutes, seconds and the number of frames on each video frame.

In the videofluoroscopic test volunteers and patients performed non-cued swallows, in duplicate, of 5 mL and 10 mL liquid and paste boluses. Liquid bolus was a liquid barium sulfate (Bariogel® 100%, laboratory Cristália, Itapira, São Paulo, Brazil) which was given to the individuals by a graduate syringe, and the paste bolus was prepared with 30 mL of liquid barium mixed with 3 g of food thickner Nutilis (Cuyk Nutricia BV, Cuyk, The Netherlands) given to the individuals using a spoon. The test was performed with subjects in the sitting position and images of the mouth, pharynx and proximal esophagus captured in right-lateral position. The liquid bolus was classified as level 3 (moderately thick) and the paste bolus as level 4 (extremely thick) according to the flow test proposed by the International Dysphagia Diet Standardization Initiative (IDDSI)[11].

It were timed the onset of propulsive tongue tip movement at the maxillary incisors, passage of the bolus head through the fauces, passage of the bolus tail through the fauces, onset and end of hyoid movement, onset and offset of upper esophageal sphincter (UES) opening.

These times were used to calculate oral and pharyngeal transit time: oral transit time – tongue tip at incisors to passage of the bolus tail through the fauces; pharyngeal transit time – bolus tail at fauces to offset of the UES opening; pharyngeal clearance – bolus head at fauces to the offset of the UES opening; UES opening (transit) – time interval between the onset and offset of UES opening; duration of hyoid movement – time interval between the beginning and end of hyoid movement; oropharyngeal transit time – tongue tip at incisors to the offset of the UES opening.

Statistical analysis was performed by a linear mixed-effects model (random and fixed effects)[12]. The model adjustment was done using proc mixed of SAS version 9.2[13]. The results are reported as means and standard deviations (SD), in seconds, unless otherwise stated.

RESULTS

There was no difference in oral or pharyngeal transit duration between FH and controls with liquid (TABLE 1) and paste (TABLE 2) swallows.

No aspiration of bolus into the airways was detected in any individual. Pharyngeal residues were detected in 12.5% of swallows in patients and 15.0% of swallows in controls, after swallows of 10 mL paste bolus (P>0.10).

DISCUSSION

Our findings in patients with FH lead different conclusions to those described in patients with GERD. In GERD it takes longer for the bolus to move from the pharynx to the proximal esophagus[6,7]. As FH patients have symptoms but do not have excessive esophageal acidic exposure, the results suggested that the pres-

TABLE 1. Oral and pharyngeal transit time, in seconds, in patients with functional heartburn (FH, n=8) and controls (n=12), after 5 mL and 10 mL liquid swallows. Mean (SD).

	5 mL			10 mL		
	Controls	FH	*P*-value	Controls	FH	*P*-value
OTT	0.66 (0.33)	0.62 (0.22)	0.82	0.48 (0.19)	0.59 (0.39)	0.67
PTT	0.39(0.10)	0.41 (0.12)	0.68	0.38 (0.10)	0.34 (0.11)	0.28
PC	0.70 (0.19)	0.77 (0.19)	0.31	0.70 (0.16)	0.66 (0.14)	0.50
HM	0.91(0.30)	0.90 (0.27)	0.92	0.79 (0.19)	0.79 (0.16)	0.99
UESO	0.41 (0.10)	0.40 (0.13)	0.59	0.46 (0.12)	0.45 (0.11)	0.78
OPTT	1.07 (0.33)	1.03 (0.29)	0.77	0.87 (0.22)	0.76 (0.25)	0.15

OTT: oral transit time; PTT: pharyngeal transit time; PC: pharyngeal clearance; HM; hyoid movement; UESO: upper esophageal sphincter opening; OPTT: oropharyngeal transit time.

TABLE 2. Oral and pharyngeal transit time, in seconds, in patients with functional heartburn (FH, n=8) and controls (n=12), after 5 mL and 10 mL swallows of paste bolus. Mean (SD).

	5 mL			10 mL		
	Controls	FH	*P*-value	Controls	FH	*P*-value
OTT	0.73 (0.42)	1.21 (1.13)	0.24	0.67 (0.43)	0.95 (0.87)	0.37
PTT	0.45 (0.18)	0.41 (0.10)	0.52	0.47 (0.27)	0.57 (0.43)	0.64
PC	0.78 (0.36)	0.71 (0.44)	0.49	0.85 (0.46)	1.06 (0.55)	0.24
HM	1.00(0.13)	1.00 (0.36)	0.87	0.91 (0.53)	1.14 (0.43)	0.15
UESO	0.38 (0.11)	0.35 (0.12)	0.45	0.47 (0.16)	0.55 (0.33)	0.47
OPTT	1.21 (0.44)	1.63 (1.08)	0.28	1.15 (0.58)	1.48 (0.91)	0.24

OTT: oral transit time; PTT: pharyngeal transit time; PC: pharyngeal clearance; HM; hyoid movement; UESO: upper esophageal sphincter opening; OPTT: oropharyngeal transit time.

ence of acid inside the esophagus in GERD may cause functional changes in the upper digestive tract. Although there are few reports on these alterations, we may speculate that these changes occur mainly in the UES[7,14,15], and due to the presence of superficial esophageal mucosal afferent nerves in cases of NERD[16]. In FH, afferent nerves are deep within the esophageal mucosa, more alike with that of healthy individuals[17], and the esophagus is more sensitive to mechanical than acid stimuli[4,5], i.e., esophageal distention and smooth muscle contraction[4]. It is important to consider that many symptoms attributed to gastroesophageal reflux, may be caused by a group of syndromes of different pathophysiologies[18].

The slower pharyngeal and UES transit time may be one of the causes of dysphagia in patients with GERD, a complaint reported by almost half of the patients[7-9]. However, these changes do not explain the symptom of dysphagia reported by 62.5% of patients with FH in this investigation. Esophageal hypersensitivity to both acid and mechanical stimuli is a possible explanation for dysphagia in these patients[4,5].

Heartburn in FH is not related with episodes of gastroesophageal reflux. Then, suggests the occurrence of esophageal hypersensitivity to esophageal distention and/or smooth muscle contraction, but abnormalities in the central nervous system cannot be ruled out. The transient potential vanilloid subtype 1 receptor (TRPV1) is involved in esophageal hypersensitivity in these patients[4].

There is no good evidence to support the use of neuromodulators or psychological interventions in FH, to address the gut-brain axis disturbance associated with the disease[5]. TRPV1 antagonists would be a possibility in this sense[4]. The treatment should be tailored taking in consideration the pathophysiology and manifestations of each member of the gastroesophaeal reflux syndrome. Proton pump inhibitors is not always the best choice for the treatment of FH, as it may result in over usage of antisecretory agents[18]. In addition, anxiety, hypervigilance, visceral and central hypersensitivity have modulating effects on symptom severity which should be considered in a personalized approach to managing FH patients[18].

This investigation has some limitations. The number of patients with FH was small, however it was enough to draw valid conclusions about oral and pharyngeal transit. The inclusion criteria of patients with FH cause some limitations, in terms of diagnosis and duration of the disease. Our study group was composed of women only, since these were the patients treated for FH at the Division of Gastroenterology of the hospital during the time of investigation. Gender is known to influence videofluoroscopic results[19], and the control group was composed for women only. Finally, the effects of aging on oral-pharyngeal transit time has been recently reviewed[20]. The conclusion was that bolus transit times do not appear to change with age, however tended to have a delayed swallow response times and longer duration of UES opening. In this investigation no difference of the swallowing transit duration was found between patients and controls, thus the possibility that the age has influence on the results is not likely. The influence of aging on the swallowing is seen mainly in individuals older than 70 years old[20].

In conclusion, in this investigation oral and pharyngeal transit time of patients with FH did not differ from that of healthy volunteers.

Authors' contribution

Cassiani RA and Dantas RO had participation in study planning, investigation, data collection and discussion of results, in addition to manuscript preparation and in decision to submit to publication.

Orcid

Rachel Aguiar Cassiani: 0000-0002-6100-7025.
Roberto Oliveira Dantas: 0000-0003-2183-0815.

Cassiani RA, Dantas RO. Trânsitos oral e faríngeo na pirose funcional. Arq Gastroenterol. 2020;57(2):150-3.

RESUMO – **Contexto** – A doença do refluxo gastroesofágico está associada ao trânsito mais lento do bolo deglutido pela faringe e esfíncter superior do esôfago. Pirose funcional tem sintomas similares aos de doença do refluxo gastroesofágico, entretanto eles não são consequência de refluxo. **Objetivo** – Como na pirose funcional os sintomas são semelhantes aos da doença do refluxo gastroesofágico, o objetivo desta investigação foi avaliar a duração do trânsito do bolo deglutido pela boca, faringe e esfíncter superior do esôfago em pacientes com pirose funcional, com a hipótese de que esses pacientes também apresentem alteração no trânsito. **Métodos** – Pelo método videofluoroscópico foi avaliado o trânsito oral e faríngeo de oito pacientes do sexo feminino com pirose funcional, cinco com disfagia leve para alimentos sólidos, e 12 indivíduos controles do sexo feminino. Controles e pacientes deglutiram em duplicata 5 mL e 10 mL de bolos com a consistências líquida e pastosa. **Resultados** – Com bolo líquido e pastoso não houve diferença na duração do trânsito oral, faríngeo e pelo esfíncter superior do esôfago entre controles e pacientes. Não houve aspiração do bolo para as vias aéreas em nenhum indivíduo. Os resíduos faríngeos foram observados na mesma proporção das deglutições em pacientes (12,5%) e controles (15%), com a deglutição de 10 mL de bolo pastoso. **Conclusão** – A duração do trânsito oral, faríngeo e pelo esfíncter superior do esôfago foi semelhante nos pacientes com pirose funcional e controles.

DESCRITORES – Azia. Deglutição. Esfíncter esofágico superior. Refluxo gastroesofágico.

REFERENCES

1. Kandulski A, Moleda L, Müler-Schilling M. Diagnostic investigations of gastroesophageal reflux disease; who and when to refer and for what test? Visc Med. 2018;34:97-100.
2. Aziz Q, Fass R, Gyawali CP, Miwa H, Pandolfino JE, Zerbib F. Esophageal disorders. Gastroenterology. 2016;150:1368-79.
3. Hachem C, Shaheen N. Diagnosis and management of functional heartburn. Am J Gastroenterol. 2016;111:53-61.
4. Kondo T, Miwa H. The role of esophageal hypersensitivity in functional heartburn. J Clin Gastroenterol. 2017;51:571-8.
5. Lee YY, Wu JCY. Management of patients with functional heartburn. Gastroenterology. 2018;154:2018-21.
6. Mendell DA, Logemann JA. A retrospective analysis of the pharyngeal swallow in patients with clinical diagnosis of GERD compared with normal controls: a pilot study. Dysphagia. 2002;17:220-6.
7. Cassiani RA, Mota GA, Dantas RO. Oral and pharyngeal transit in gastroesophageal reflux disease. Esophagus. 2015;12:345-51.
8. Vakil NB, Traxler B, Levine D. Dysphagia in patients with erosive esophagitis: prevalence, severity, and response to proton pump inhibitor treatment. Clin Gastroenterol Hepatol. 2004;2:665-8.
9. Triadafilopoulos G. Nonobstructive dysphagia in reflux esophagitis. Am J Gastroenterol. 1989;84:614-8.
10. Kidambi T, Toto E, Ho N, Taft T, Hirano I. Temporal trends in the relative prevalence of dysphagia in reflux esophagitis. World J Gastroenterol. 2012;18:4335-41.
11. Cichero JAY, Lam P, Steele CM, Hanson B, Chen J, Dantas RO, et al. Development of international terminology and definitions for texture-modified foods and thickened fluids used in dysphagia management. The IDDSI framework. Dysphagia. 2017;32:293-314.
12. Schall R. Estimation in generalized linear models with random effects. Biometrika. 1991;78:719-27.
13. Littell RC, Milliken GA, Stroup WW, Wolfinger RD. SAS system of non-linear mixed models. Cary, NC: SAS Institute Inc.; 1996.
14. Dantas RO, Cassiani RA. Upper esophageal sphincter dysfunction in gastroesophageal reflux disease. Dysphagia. 2019;34:942-3.
15. Nativ-Zeltzer N, Rameau A, Kun MA, Kaufman M, Belafsky PC. The relationship between hiatal hernia and cricopharyngeus dysfunction. Dysphagia. 2019; 34:391-6.
16. Woodland P, Shen Ooi JL, Grassi F, Nikaki K, Lee C, Evans JA, et al. Superficial esophageal mucosal afferent nerves may contribute to reflux hypersensitivity in nonerosive reflux disease. Gastroenterology. 2017;153:1230-9.
17. Nikaki K, Woodland P, Lee C, Ghisa M, Martinelli C, Savarino E, et al. Esophageal mucosal innervation in functional heartburn: closer to healthy asymptomatic subjects than to non-erosive reflux disease. Neurogastroenterol Motil. 2019;31:e13667.
18. Katzka DA, Pandolfino JE, Kahrilas PJ. Phenotypes of gastroesophageal reflux disease: where Rome, Lyon, and Montreal meet. Clin Gastroenterol Hepatol. 2020;18:767-76.
19. Dantas RO, Cassiani RA, Santos CM, Gonzaga CG, Alves LMT, Mazin SC. Effect of gender on swallow duration assessed by videofluoroscopy. Dysphagia. 2009;24:280-4.
20. Namasivayam-MacDonald AM, Barbon CEA, Steele CM. A review of swallow timing in the elderly. Physiol Behav. 2018;184:12-6.

ORIGINAL ARTICLE

AG-2019-165
doi.org/10.1590/S0004-2803.202000000-29

Diagnostic accuracy of GastroPanel® for atrophic gastritis in Brazilian subjects and the effect of proton pump inhibitors

Rejane **MATTAR**[1], Sergio Barbosa **MARQUES**[2], Igor Braga **RIBEIRO**[2], Thiago Arantes de Carvalho **VISCONTI**[2], Mateus **FUNARI**[2] and Eduardo Guimarães Hourneaux **DE MOURA**[2]

Received: 29 November 2019
Accepted: 9 January 2020

ABSTRACT – **Background** – It has been proposed that the combination of gastrin-17 (G-17), pepsinogens I and II (PGI and PGII), and anti-*Helicobacter pylori* (*H. pylori*) antibodies (GastroPanel®, BIOHIT HealthCare, Helsinki, Finland) could serve as biomarkers of atrophic gastritis. **Objective** – This study aimed to ensure the diagnostic accuracy of GastroPanel® and evaluate the effect of proton pump inhibitors (PPIs) on these biomarkers. **Methods** – Dyspeptic patients who underwent gastrointestinal endoscopy were enrolled in the present study. Histological findings, which were the gold standard to stratify groups, were as follows: no atrophy (controls); antrum atrophy; corpus atrophy; multifocal atrophy; and neoplasia. G-17, PGI, PGII, and anti-*H. pylori* immunoglobulin (Ig)G antibodies were assayed using commercially available kits. The ratio of PGI/PGII was calculated. **Results** – Among 308 patients, 159 (51.6%) were PPI users. The overall prevalence of atrophy was 43.8% (n=135). Ninety-two (29.9%) patients were *H. pylori* positive according to anti-*H. pylori* IgG levels. G-17 levels were not low in those with antrum atrophy but were high in those with corpus and multifocal atrophies. PGI levels were significantly lower in those with corpus and multifocal atrophies. The sensitivity of PGI <30 µg/L to detect corpus atrophy was 50% (95% CI 27.8–72.1%), with a specificity of 93.2% (95% CI 84.3–97.5%), a positive likelihood ratio of 7.4 (95% CI 2.9–19.2), and a negative likelihood ratio of 0.5 (95% CI 0.3–0.8). A small number of subjects (n=6) exhibited moderate to intense atrophy (4%), among whom 66.7% exhibited decreased PGI levels. PPI significantly increased the levels of G-17 and PGI, except in those with corpus and multifocal atrophies, in whom PGI levels were not increased by PPIs. **Conclusion** – GastroPanel® (Gastrin-17, PGI, and PGI/PGII ratio) did not demonstrate high sensitivity for detecting gastric atrophy.

HEADINGS – Pepsinogen A. Gastrins. Atrophic gastritis. *Helicobacter pylori*.

INTRODUCTION

The natural history of *Helicobacter pylori* (*H. pylori*) infection involves inflammation of the antrum progressing into the corpus and long-term injury, resulting in the loss of normal glandular tissue, otherwise known as multifocal atrophic gastritis[1,2]. Therefore, gastric cancer associated with *H. pylori* infection is the end phase of a long evolution process including chronic, active, non-atrophic gastritis, multifocal (antrum and corpus) atrophic gastritis without intestinal metaplasia, intestinal metaplasia of the complete type, intestinal metaplasia of the incomplete type, low-grade dysplasia, high-grade dysplasia, and, finally, cancer[2]. Thus, monitoring atrophic gastritis and intestinal metaplasia using gastrointestinal endoscopy with histological examination of the antrum and corpus is performed as a preventive measure against gastric cancer. However, upper gastrointestinal endoscopy with gastric biopsy is invasive and not accessible to all asymptomatic individuals. Thus, serological assays to detect gastric atrophy and intestinal metaplasia are essential for the early diagnosis of gastric cancer[3].

Other causes of gastric atrophy, limited to the oxyntic mucosa, include autoimmunity associated with pernicious anemia with normal antral mucosa that is not involved in the pre-cancerous cascade; however, it carries an increased risk for gastric cancer and is correlated with lower levels of pepsinogen[2]. *H. pylori* infection may trigger autoimmune gastritis by molecular mimicry between its antigens and gastric H/K ATPase[4].

Mature gastrin is synthetized by endocrine G cells of the gastric antrum in the presence of proteins and calcium in the stomach lumen. Neutralization or inhibition of acid by drugs or corpus atrophy induces the release of gastrin. After expression of the gastrin gene, the messenger RNA is translated into progastrin, which is processed along its passage through the Golgi complex, resulting in G-34 (predominant in the duodenum) and G-17 (predominant in the antrum), which are able to stimulate gastric acid secretion. Gastrin acts on the gastrin receptors on enterochromaffin cells of the gastric fundus to release histamine, which, in a paracrine action, binds to the H_2 receptors on parietal cells with the output of H^+, Cl^-, and H_2O. Other stimuli include acetylcholine and gastrin, which can directly act on the surface receptors on parietal cells and stimulate acid secretion[5-7].

Declared conflict of interest of all authors: none
Disclosure of funding: no funding received
[1] Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, Divisão de Gastroenterologia e Hepatologia Clínica, São Paulo, SP, Brasil. [2] Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, Divisão de Endoscopia, São Paulo, SP, Brasil.
Corresponding author: Rejane Mattar. E-mail: r.mattar@hc.fm.usp.br

PGI and PGII are secreted by the chief cells of the oxyntic glands in the fundus and corpus. PGII is also secreted by the pyloric glands in the antrum and glands of Brunner in the proximal duodenum. Pepsinogens are stored in the form of granules and secreted into the stomach lumen in response to specific stimuli. Gastric acid converts pepsinogens into the active protein digestive enzyme, pepsin[8]; only 1% of secreted pepsinogens enter the blood stream[9]. The levels of pepsinogens are high in individuals with *H. pylori*-positive non-atrophic gastritis and decrease as inflammatory changes progress, leading to damage and loss of the gastric glands, otherwise known as atrophy[2]. Accordingly, the loss of oxyntic glands in corpus atrophy would decrease PGI levels and the PGI/PGII ratio[2,3,9-11], and antrum atrophy would decrease G-17 levels[12,13].

The performance of GastroPanel® (BIOHIT HealthCare, Helsinki, Finland) in measuring G-17, PGI, PGII, and anti-*H. pylori* antibodies has not been assessed in Brazil. Therefore, the purpose of the present study was to evaluate the diagnostic accuracy of GastroPanel® and estimate the effect of proton pump inhibitor (PPI) use on these biomarkers.

METHODS

Study population

This prospective study included consecutive dyspeptic patients who attended the gastrointestinal endoscopy division between March 2017 and July 2018. Of 340 subjects from whom blood was collected, 32 were excluded (three had underwent partial gastrectomy and 29 did not have biopsies taken according to the OLGA protocol)[14], leaving 308 subjects eligible for the study, 216 (70.1%) of whom were women. The mean (±SD) age of the study cohort was 64.6±10.3 years (range, 29 to 87 years). Individuals with systemic and psychiatric diseases, those who underwent gastrectomy, used anticoagulant drugs, and those in whom no biopsy samples were taken according to the OLGA protocol[14] were excluded. Patients answered a questionnaire surveying their consumption of medications (PPIs and H_2 receptor antagonists); those who were using PPIs were stratified separately from non-PPI users. The criteria to consider patients as non-PPI users was to have discontinued PPI and H_2 receptor antagonists for at least two weeks before testing. Individuals who underwent previous *H. pylori* eradication treatment were included. The questionnaire had no questions to select subjects with autoimmune gastritis or neuroendocrine tumors.

Ethical statement

The Ethics Committee of the Hospital approved this study protocol under the CAAE: 50561715.5.0000.0068, and all subjects provided informed written consent to participate.

Gastrointestinal endoscopy

After a 12-h fast, simethicone solution was used to improve the visibility of the mucosa, followed by 10% xylocaine spray and intravenous sedation with midazolam, fentanyl, and propofol, as previously described[15]. Endoscopies were initially performed using a standard endoscope (GIF-H180, Olympus Co., Miami, FL, USA) using white light. Subsequently, narrow-band imaging (NBI) was activated, which facilitated visualization of the mucosa and re-evaluation for the detection of macroscopically visible abnormalities. Five gastric mucosa samples were obtained according to the OLGA sampling protocol (from the corpus C1 and C2, antrum A1, A2, and the incisura angularis A3)[14], as well as from lesions detected macroscopically and by NBI.

GastroPanel® analysis

G-17, PGI, PGII, and anti-*H. pylori* IgG antibody levels were assayed using monoclonal antibodies and commercially available enzyme immunoassay kits (BioHit, Helsinki, Finland). The ratio of PGI/PGII was also calculated. Blood samples were collected in EDTA vials and centrifuged; the plasma was stored frozen until testing. Blood collection was performed at the gastrointestinal endoscopy division before sedation. Initially, the samples were diluted with diluent buffer for the assays as follows: 1:5 for G-17; 1:20 for PGI and PGII; and 1:400 for *H. pylori*. The blank solutions (for G-17, PGI, and PGII) or the sample diluent buffer (for *H. pylori*), calibrators, controls, and diluted samples were pipetted into microplate wells at a volume of 100 µL. The microplates were incubated at room temperature for 60 min with shaking (750 rpm). The microplate strips were washed three times with 350 µL of diluted wash buffer, inverted, and gently tapped a few times on a clean paper towel. Specific conjugate solutions (100 µL) were subsequently pipetted into the microplate wells and incubated for 60 min at room temperature with shaking (750 rpm). The microplate strips were washed three times with 350 µL of diluted wash buffer, inverted, and gently tapped a few times on a clean paper towel. Substrate solution (100 µL) was subsequently pipetted into the microplate wells and incubated for 30 min at room temperature while protected from light. Finally, 100 µL of stop solution was pipetted into the microplate wells. The absorbance of the microplate wells was measured at 450 nm using a microplate reader (Vivid Vision, ALKA Tecnologia, São Paulo, Brazil). Reference ranges according to the manufacturer were as follows: G-17 (1–7 pmol/mL); PGI (30–160 µg/L); PGII (3–15 µg/L); PGI/PGII ratio (3–20); and *H. pylori* IgG (<30 EIU). PGI was considered to have decreased at levels <30 µg/L, and the PGI/PGII ratio was considered to have decreased if <3. *H. pylori* IgG >30 EIU indicated positive *H. pylori* infection, although the assay did not discriminate current from pre-existing exposure to the bacteria[16].

Histological examination

Biopsy samples were fixed in 10% formalin and stained with hematoxylin and eosin for histological diagnosis, based on the updated Sydney System[17]; *H. pylori* was identified using Giemsa stain, indicating current infection[16]. Histological findings were considered to be the gold standard used to stratify subjects into the following categories: no atrophy, including chronic active and chronic inactive gastritis (controls); antrum and/or incisura angularis atrophy (antrum group); antrum and corpus atrophy (multifocal group); and corpus atrophy (corpus group). The neoplasia group consisted of patients who were analyzed together, with gastric cancer, mucosal low-grade neoplasia, and neuroendocrine tumor. Based on histological findings using the updated Sydney System[17], the OLGA stages[14] were determined.

Statistical analyses

Statistical analyses of categorical variables were performed using SPSS version 15.0 (SPSS, Chicago, IL, USA) for Windows (Microsoft Corporation, Redmond, WA, USA) and Fisher's exact test; differences with $P<0.05$ were considered to be statistically significant. Subjects with no atrophy were considered as the controls with which all other groups were compared. Diagnostic accuracy was determined among subjects who were non-PPI users. Each group of PPI users was compared with the non-PPI users. The levels of biomarkers were compared between the controls and the

other groups using the Mann-Whitney test. Sensitivity, specificity, positive predictive value, negative predictive value, and positive and negative likelihood ratios with 95% confidence interval (95% CI) were calculated using an online program (http://vassarstats.net/). According to McNicholl et al. (2014)[18] who analyzed the accuracy of GastroPanel® for the diagnosis of atrophic gastritis, a sample size of 90 was calculated, as they considered the prevalence of chronic atrophic gastritis to be 23% and that 20 patients would have chronic atrophic gastritis. In the present investigation, G* Power version 3.1.9.4 (Franz Faul, Universität Kiel, Germany) was used to for *post hoc* power analysis. The effect size was calculated with the means and standard deviations between two groups. The result of effect size was transferred to main window to calculate power (1- β error probability) for each one of the analysis of the study by means: Wilcoxon-Mann Whitney test (two groups). The input parameters were the effect size d, α=0.05, sample size of group 1 and sample size of group 2 to calculate power for each one of the analysis. Results are reported in accordance with the Standards for the Reporting of Diagnostic accuracy studies (STARD) checklist (2015)[19].

RESULTS

Endoscopy yielded the following findings: normal endoscopy, mild esophagitis, or minor changes, n=68 (22.1%); gastroduodenal erosions, n=78 (25.3%); atrophy, n=106 (34.4%); suspicious gastric lesions, n=7 (2.3%); gastric cancer, n=11 (3.6%); gastric ulcer, n=15 (4.9%); gastric polyps, n=15 (4.9%); and duodenal ulcer, n=8 (2.6%).

A diagram illustrating patient flow though the study, based on histological findings, is presented in FIGURE 1. Among the 308 patients, 159 were PPI users (51.6%). The overall prevalence of atrophy was 43.8% (n=135). Five groups were categorized according to the histological diagnoses as follows: controls, n=158 (non-PPI users, n=74; PPI users, n=84); antrum atrophy, n=72 (non-PPI users, n=29; PPI users, n=43); multifocal (antrum and corpus) atrophy, n=34 (non-PPI users, n=19; PPI users, n=15); corpus atrophy, n=29 (non-PPI users, n=20; PPI users, n=9); and neoplasia, n=15. The neoplasia group consisted of nine patients with gastric cancer (three non-PPI users; six PPI users), three with mucosal low-grade neoplasia (only one non-PPI user) and three with neuroendocrine tumor (all non-PPI users). Among patients with gastric cancers, three were diagnosed with poorly differentiated carcinoma, three with moderately differentiated carcinoma, and three with well-differentiated carcinoma.

H. pylori was positive in 92 (29.9%) subjects according to anti-*H. pylori* IgG levels, and in 61 (19.8%) according to Giemsa staining of gastric samples**.** *H. pylori* infection was positive in 25.8% of the subjects who used PPIs and in 34.2% of non-PPI users. The highest prevalence of *H. pylori* infection (51.7%, $P<0.05$) was in the antrum atrophy group of non-PPI users (data not shown), who also exhibited significantly higher levels of anti-*H. pylori* IgG (power=0.70) (FIGURE 2).

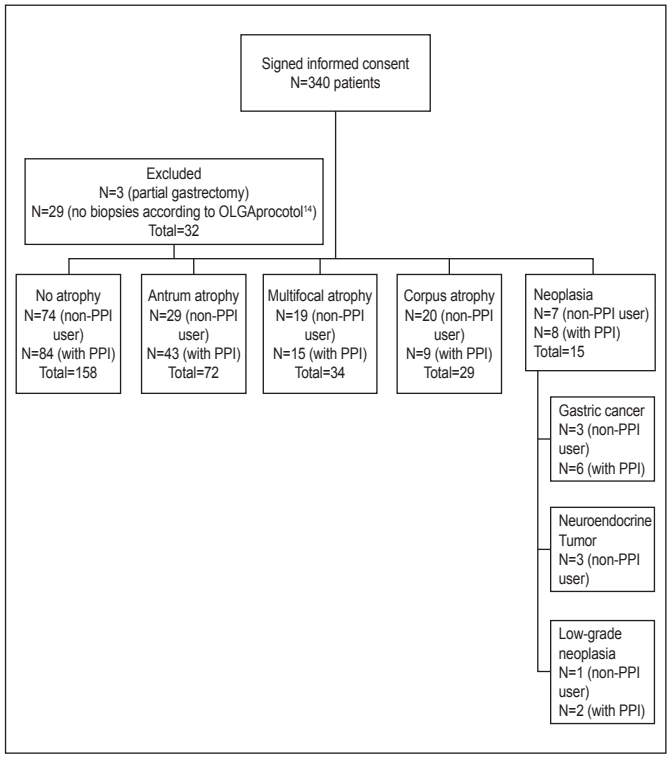


FIGURE 1. Flow chart of the subjects eligible for the study.
PPI: proton pump inhibitor.

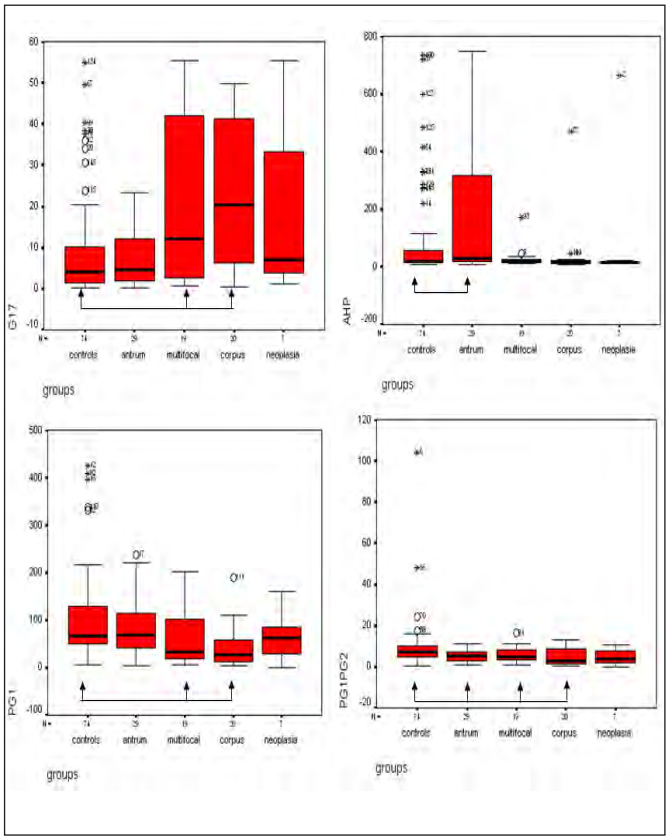


FIGURE 2. Comparison of the levels of G-17 (pmol/mL), PGI (μg/L), anti-*H. pylori* Ig(G) (EIU), and the PGI/PGII ratio of each group of non-PPI users with the controls.
The arrows indicate significance between the group and controls. The graphs indicate the medians and the boxes the 25%–75% quartiles.
$P<0.05$: statistically significant; PG1: PGI; PG2: PGII; PG1/PG2: PGI/PGII; AHP: anti-*H. pylori* Ig(G); Antrum: antrum atrophy; Multifocal: multifocal atrophy; Corpus: corpus atrophy.

G-17 levels were significantly higher in those with corpus (power=0.98) and multifocal (power=0.93) atrophies; however, was not lower in antrum atrophy (power=0.26). PGI was significantly lower in corpus (power=0.91) and multifocal (power=0.59) atrophies. The PGI/PGII ratio was significantly lower in all groups, except for neoplasia (antrum atrophy; power=0.66, multifocal atrophy; power=0.43, and corpus atrophy; power=0.58) compared with controls (FIGURE 2). There were no significant differences in the levels of biomarkers between women and men (data not shown). Age was not significantly different among controls and the atrophy groups (data not shown).

The performance of PGI (<30 µg/L) and PGI/PGII ratio (<3) to detect gastric atrophy with 95% confidence interval (CI) is summarized in TABLE 1 for corpus and multifocal atrophy groups. For corpus atrophy, PGI < 30 µg/L demonstrated a sensitivity of 50% (95% CI 27.8–72.1%), a specificity of 93.2% (95% CI 84.3–97.5%), a positive predictive value of 15.9% (95% CI 9.5–25.3%), a negative predictive value of 84% (95% CI 74.7–90.5%), and positive 7.4 (95% CI 2.9–19.2) and negative 0.5 (95% CI 0.3–0.8) likelihood ratios. The PGI/PGII ratio of <3 demonstrated a sensitivity of 55% (95% CI 32–76.2%), a specificity of 93.2% (95% CI 84.3–97.4%), a positive predictive value of 17% (95% CI 10.3–26.5%), a negative predictive value of 82.9% (95%CI 73.5–89.7%), and positive 8.1 (95% CI 3.2–20.7) and negative 0.5 (95% CI 0.3–0.8) likelihood ratios.

For multifocal atrophy, PGI <30 µg/L demonstrated a sensitivity of 42.1% (95% CI 21.1–66%), a positive predictive value of 13.9% (95% CI 7.9–23%), a negative predictive value of 86% (95% CI 76.9–92%), and positive 6.2 (95% CI 2.3–16.9) and negative 0.6 (95% CI 0.4–0.9) likelihood ratios. PGI/PGII ratio of <3 demonstrated a sensitivity of 21% (95% CI 6.9–46%), a positive predictive value of 9.7% (95% CI 5–18%), a negative predictive value of 90.3% (95% CI 81.9–95.2%), and positive 3.1 (95% CI 0.9–10.5) and negative 0.8 (95% CI 0.7–1.0) likelihood ratios.

The distribution of subjects who were non-PPI users according to the OLGA stage revealed that 75 (50.3%) were stage O, 68 (45.6%) stages I–II, and six (4%) stages III–IV. The PGI level was <30 µg/L in 19 (27.9%) subjects with stages I and II and four (66.7%) with stages III and IV (P<0.05) (TABLE 2). Among the subjects who exhibited gastric atrophy, 87 (58.4%) exhibited no intestinal metaplasia.

TABLE 1. The performance of PGI (<30 µg/L) and PGI/PGII ratio (<3) to detect gastric atrophy with 95% confidence interval for corpus and multifocal atrophy (non-PPI users) groups.

Parameters	PGI <30 µg/L	PGI/PGII ratio<3
Sensitivity		
Corpus atrophy	50% (27.8–72.1%)	55% (32–76.2%)
Multifocal atrophy	42.1% (21.1–66%)	21% (6.9–46%)
Specificity	93.2% (84.3–97.5%)	93.2% (84.3–97.4%)
PPV		
Corpus atrophy	15.9% (9.5–25.3%)	17% (10.3–26.5%)
Multifocal atrophy	13.9% (7.9–23%)	9.7% (5–18%)
NPV		
Corpus atrophy	84% (74.7–90.5%)	82.9% (73.5–89.7%)
Multifocal atrophy	86% (76.9–92%)	90.3% (81.9–95.2%)
+ Likelihood ratio		
Corpus atrophy	7.4 (2.9–19.2)	8.1 (3.2–20.7)
Multifocal atrophy	6.2 (2.3–16.9)	3.1 (0.9–10.5)
– Likelihood ratio		
Corpus atrophy	0.5 (0.3–0.8)	0.5 (0.3–0.8)
Multifocal atrophy	0.6 (0.4–0.9)	0.8 (0.7–1)

TABLE 2. PGI results according to OLGA stages of subjects who were non-PPI users.

OLGA	PGI <30 µg/L	PGI ≥30 µg/L	Total
Stage 0	5 (6.7%)	70 (93.3%)	75 (50.3%)
Stages I and II	19 (27.9%)	49 (72.1%)	68 (45.6%)
Stages III and IV	4 (66.7%)	2 (33.3%)	6 (4%)
Total	28 (18.8%)	121 (81.2%)	149 (100%)

P<0.05.

Comparison of the levels of G-17, PGI, anti-*H. pylori* IgG, and the PGI/PGII ratio of each group of PPI-users with its counterpart non-PPI users (FIGURE 3) revealed that PPI use significantly increased the levels of G-17 in controls (power=0.97) and

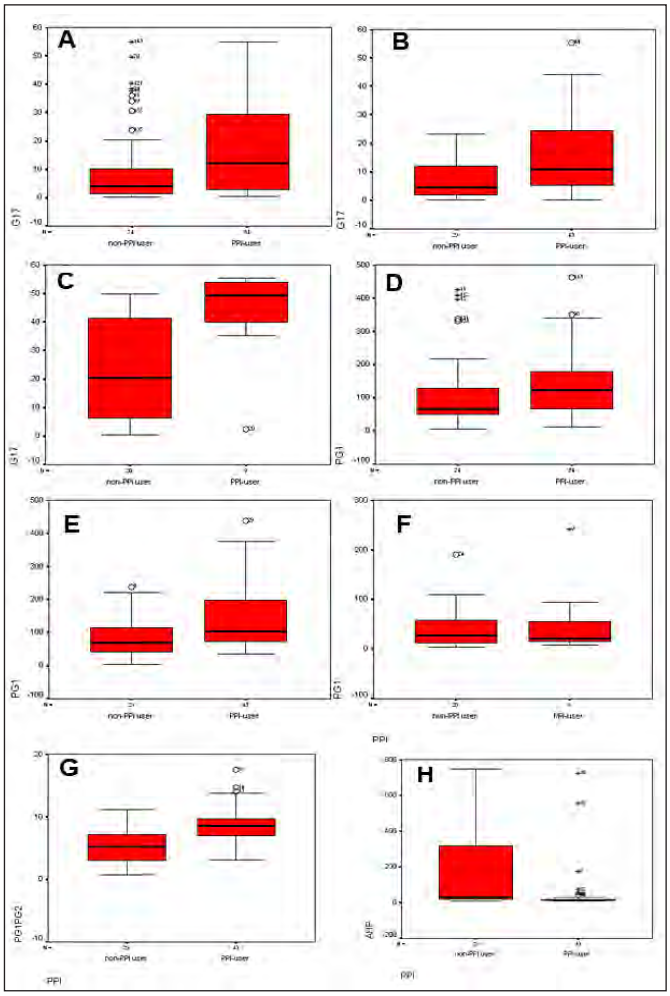


FIGURE 3. Comparison of the levels of G-17 (pmol/mL) and PGI (µg/L) of PPI-users with its counterpart non-PPI users in controls (A, D), corpus atrophy (C, F) and antrum atrophy (B, E, G, H) and anti-*H. pylori* Ig(G) (EIU), and the PGI/PGII ratio in antrum atrophy.
The graphs indicate the medians and the boxes the 25%–75% quartiles. PG1: PGI; PG1/PG2: PGI/PGII; AHP: anti-*H. pylori* Ig(G); PPI: Proton pump inhibitors.
A, B, C, D, E, G, H: P<0.05; F: P>0.05.

in those with corpus atrophy (power=0.81) and antrum atrophy (power=0.95). PPI use did not increase the levels of PGI in corpus atrophy (power=0.11) and in multifocal atrophy (power=0.25) (data not shown); however, increased the levels of PGI in controls (power=0.78) and in those with antrum atrophy (power=0.89). The PGI/PGII ratio was significantly higher in the antrum atrophy group that were PPI-users in relation to the antrum group that were non-PPI users (power= 0.99). The levels of anti-*H. pylori* IgG were significantly higher in the antrum atrophy non-PPI user group compared with the antrum atrophy PPI user group (power=0.87).

DISCUSSION

The simultaneous quantification of G-17, PGI, PGII, and anti-*H. pylori* IgG levels using GastroPanel® was designed in the late 1990s to evaluate the structure and function of the entire stomach mucosa, antrum, and corpus. Since then, several studies from different countries have tested GastroPanel®, mainly in dyspeptic subjects with atrophic gastritis, to ascertain its application as a noninvasive screening test for pre-neoplastic conditions in gastric cancer[11]. GastroPanel® is not indicated for diagnosing gastric cancer but for selecting subjects with atrophic gastritis in whom gastrointestinal endoscopy is necessary to search for cancerous lesions[3,9,11,16].

The purpose of the present study was to evaluate the utility of the serological markers G-17, PGI, PGII, and the ratio of PGI/PGII for the diagnosis of gastric atrophy, to identify individuals who should undergo upper gastrointestinal endoscopy. The overall prevalence of gastric atrophy (43.8%) was higher than the median prevalence of atrophic gastritis (27%) across studies described elsewhere[3]. The prevalence of intestinal metaplasia in countries around the world increases with age and the presence of *H. pylori* infection and is as high as 45.2% in the elderly in the high-risk gastric cancer region of Colombia[20]. Moreover, gastric atrophy in Japan and China may reach prevalences >50%[21]. Atrophy and intestinal metaplasia tend to be more common among elderly individuals in most studies, reflecting a progression of gastritis with age[3,9,20,21]; however, age was not significantly different among controls and the atrophy groups. There were no statistically significant differences between women and men, although women with atrophy were found to have a lower risk for developing gastric cancer than men[21].

Unexpectedly, the prevalence of *H. pylori* infection (29.9%) was lower than that in 2005 (53%)[22], except for the non-PPI group with antrum atrophy which had the significantly highest prevalence (51.7%) similar to that report[22]. *H. pylori* eradication regimens have since been widely used. The difference in the prevalence of *H. pylori* infection (29.9%) according to the serological assay and Giemsa stain (19.8%) may be due to over-diagnosis in the serological assay, which does not discriminate current from previous infection[16]. Nevertheless, serology has the advantage of not being affected by changes in bacterial load in the stomach from the action of antisecretory drugs or recent antimicrobial treatment that may lead to false-negative results in other tests[16].

G-17, which is secreted into the circulation only by G cells in the antrum, may indicate atrophy in the antrum of the stomach because the loss of G cells due to the atrophy process should reduce the levels of G-17[3,5,10-13]. However, the regulation of levels of G-17 are far more complex, as gastric acid output downregulates G-17 levels when is high and upregulates when is low[5]. Consequently, prolonged use of PPIs[23] and corpus atrophy tend to increase G-17 levels[10,11]. In fact, the use of PPIs significantly increased G-17 levels among the controls and the antrum and corpus atrophy groups as a result of hypochlorhydria. Unexpectedly, G-17 was not significantly decreased in those with antral lesions, as previously reported[3,10]; however, other authors[12] did not describe its decrease in the antrum atrophy either. Furthermore, the levels of G-17 were significantly higher in those with corpus and multifocal lesions due to an upregulation of G-17 by low acid output of the gastric glands[3,18]. Although women have significantly higher values of basal gastrin[24], statistically significant differences between men and women were not observed in the current study. Women also exhibit lower acid output than men[7], which may explain the higher levels of gastrin[24].

PGI levels were significantly lower in those with corpus atrophy and multifocal atrophy; nevertheless, sensitivities of 50% and 42.1%, respectively, were lower than those in a previous report (84%)[10] but similar to others[18] that did not recommend GastroPanel® for clinical practice. One explanation for this lower sensitivity in the present study was the small number of subjects with moderate to intense atrophy, different from the study that tested subjects with higher grades of atrophy[10].

The distribution of patients with gastric atrophy according to the OLGA stage[14] was comparable to that from Latin America, where most patients (50.2%) had OLGA stages I and II[25]. Similar to other studies[9], patients with a higher OLGA stage demonstrated a higher prevalence of decreased PGI levels; nevertheless, in this study, only 66.7% of patients with stages III and IV had decreased PGI levels. The risk for developing gastric cancer is higher in this group of patients who need to undergo endoscopy with careful follow-up[25]; therefore, the serological quantification of PGI was not accurate for atrophic gastritis screening.

The PGI/PGII ratio was significantly lower in all groups, except for neoplasia, of non-PPI users compared with controls. Conversely, the sensitivity was low (21–55%), which was in line with the results of previous reports that concluded that PGI/PGII ratio had little to no diagnostic accuracy[18]. The group with antrum atrophy, which had the highest prevalence of *H. pylori* infection, also exhibited a PGI/PGII ratio that was significantly lower than that of the controls. *H. pylori*-positive patients exhibited a lower PGI/PGII ratio[9,26] because PGI was reduced in relation to PGII, which increased due to infiltration by neutrophils and mononuclear cells in the antrum by *H. pylori* bacteria[26].

Previous studies[23] have shown that PPI use increases the levels of PGI; nevertheless, antacids/alginates or H_2 receptor antagonists did not influence G-17 and PGI serum levels. In the present study, PPIs increased the levels of PGI in controls and in the antrum atrophy group. Subjects with corpus and multifocal atrophies that were associated with decreased levels of PGI did not exhibit increased PGI levels with PPI use. The mechanism underlying the increase in PGI by PPI is unclear[8,23]; however, it has been suggested that PPIs stimulate PGI release directly from the gastric mucosa or through a gastrin link[23]. Results of the current study suggest that the corpus must be intact because, even with higher G-17 levels in corpus and multifocal atrophies, PPIs did not increase PGI levels.

The present study had limitations, including the lower sensitivity of PGI to indicate gastric atrophy compared with that of previous reports (84%)[10], which may be due to the small number of patients with moderate to intense atrophy (n=6). The group of patients with neoplasia was heterogeneous and small; however, GastroPanel® was not designed to diagnose gastric cancer. The *post*

hoc power was low for some analysis; thus, further study in a new cohort with antrum atrophy may clarify the role of G-17 reduced levels to indicate antrum atrophy, and the effect of PPI on serum levels of PGI in corpus and multifocal atrophies.

CONCLUSION

GastroPanel® (Gastrin-17, PGI, and PGI/PGII ratio) did not demonstrate high sensitivity in detecting gastric atrophy. Further studies involving a larger number of subjects with moderate to intense atrophy may improve accuracy of the results.

ACKNOWLEDGEMENTS

The authors thank Vyttra Diagnósticos for donating the kits for the study and the Department of Pathology for the histological diagnosis. The authors thank Prof. Venancio Avancini Ferreira Alves of the Department of Pathology (ICHC-FMUSP) and Alex Jones Flores Cassenote of the Epidemiology and Statistics Group of the Department of Gastroenterology (FMUSP) for comments and suggestions.

Authors' contribution

RM Mattar R: study design, ELISA tests, data management, statistics, writing the article. Marques SB: study design, patient inclusion, gastrointestinal endoscopy, collected gastric biopsy samples, data management. Ribeiro IB, Visconti TAC, Funari M: patient inclusion, gastrointestinal endoscopy, collected gastric biopsy samples. de Moura EGH and all the other authors read and approved the final version of the manuscript.

Orcid

Rejane Mattar: 0000-0001-7870-8867.
Sergio Barbosa Marques: 0000-0002-6643-6785.
Igor Braga Ribeiro: 0000-0003-1844-8973.
Thiago Arantes de Carvalho Visconti: 0000-0003-1612-1053.
Mateus Funari: 0000-0002-4828-9320.
Eduardo Guimarães Hourneaux de Moura: 0000-0002-8023-3722.

Mattar R, Marques SB, Ribeiro IB, Visconti TAC, Funari M, de Moura EGH. Acurácia diagnóstica do painel gástrico para gastrite atrófica em brasileiros e o efeito dos inibidores de bomba de prótons. Arq Gastroenterol. 2020;57(2):154-60.

RESUMO – **Contexto** – Foi proposto que a combinação de gastrina 17 (G-17), pepsinogênios I e II (PGI e PGII), e anticorpos anti-*Helicobacter pylori* (*H. pylori*) (GastroPanel®, BIOHIT HealthCare), poderiam indicar gastrite atrófica. **Objetivo** – Portanto, o objetivo foi averiguar a acurácia diagnóstica do painel gástrico e avaliar o efeito dos inibidores de bomba de prótons (IBP) nesses marcadores. **Métodos** – Pacientes dispépticos que se submeteram à endoscopia gastrointestinal entraram no estudo. Os achados histológicos foram o padrão ouro para estratificar os grupos: sem atrofia (controles), atrofia de antro, atrofia de corpo, atrofia multifocal e neoplasia. G-17, PGI, PGII, e anticorpos IgG anti-*H. pylori* foram determinados por kits comerciais. A razão PGI/PGII foi calculada. **Resultados** – Entre 308 pacientes que foram incluídos, 159 estavam usando IBP (51,6%). A prevalência de atrofia foi de 43,8% (135 pacientes). *H. pylori* foi positivo em 92 (29,9%) pacientes por IgG anti-*H. pylori*. G-17 não estava diminuída na atrofia do antro, mas estava elevada nas atrofias do corpo e multifocal. PGI estava significantemente menor nas atrofias de corpo e multifocal. A sensibilidade da PGI <30 µg/L de indicar atrofia do corpo foi 50% (95%IC 27,8–72,1%) com especificidade de 93,2% (95%IC 84,3–97,5%), razão de verossimilhança positiva de 7,4 (95%IC 2,9–19,2) e razão de verossimilhança negativa de 0,5 (95%IC 0,3–0,8). O número de indivíduos com atrofia moderada para intensa foi pequeno (n=6; 4%), dos quais 66,7% tinham diminuição dos níveis de PGI. IBP significantemente aumentou os níveis de G-17 e PGI, exceto nas atrofias de corpo e multifocal que não apresentaram aumento de PGI. **Conclusão** – O painel gástrico não teve alta sensibilidade de indicar gastrite atrófica.

DESCRITORES – Pepsinogênio A. Gastrinas. Gastrite atrófica. *Helicobacter pylori.*

REFERENCES

1. El-Zimaity HMT. Gastric atrophy, diagnosing and staging. World J Gastroenterol. 2006;12:5757-62.
2. Correa P, Piazuelo MB. The gastric precancerous cascade. J Dig Dis. 2012;13:2-9.
3. Zagari RM, Rabitti S, Greenwood DC, Eusebi LH, Vestito A, Bazzoli F. Systematic review with meta-analysis: diagnostic performance of the combination of pepsinogen, gastrin-17 and anti-*Helicobacter pylori* antibodies serum assays for the diagnosis of atrophic gastritis. Aliment Pharmacol Ther. 2017; 46:657-67.
4. Toh B-H. Diagnosis and classification of autoimmune gastritis. Autoimmun Rev. 2014;13:459-62.
5. Copps J, Murphy RF, Lovas S. The production and role of gastrin-17 and gastrin-17-gly in gastrointestinal cancers. Protein Pept Lett. 2009;16:1504-18.
6. Yao X, Forte GF. Cell biology of acid secretion by the parietal cell. Annu Rev Physiol. 2003;65:103-31.
7. Derakhshan MH, El-Omar E, Oien K, Gillen D, Fyfe V, Crabtree JE, et al. Gastric histology, serological markers and age as predictors of gastric acid secretion in patients infected with *Helicobacter pylori*. J Clin Pathol. 2006;59:1293-9.
8. Gritti I, Banfi G, Roi GS. Pepsinogens: physiology, pharmacology pathophysiology and exercise. Pharmacol Res. 2000;41:265-81.
9. Sjomina O, Pavlova J, Daugule I, Janovic P, Kikuste I, Vanags A, et al. Pepsinogen test for the evaluation of precancerous changes in gastric mucosa: a population-based study. J Gastrointestin Liver Dis. 2018;27:11-7.
10. Sipponen P, Ranta P, Helske T, Kääriääinen I, Mäki T, Linnala A, et al. Serum levels of amidated gastrin-17 and pepsinogen I in atrophic gastritis: an observational case-control study. Scand J Gastroenterol. 2002;37:785-91.
11. Syrjänen K. A panel of serum biomarkers (GastroPanel®) in non-invasive diagnosis of atrophic gastritis. Systematic review and meta-analysis. Anticancer Res. 2016;36:5133-144.
12. Leja M, Kupcinskas L, Funka K, Sudraba A, Jonaitis L, Ivanauskas A, et al. Value of gastrin-17 in detecting antral atrophy. Adv Med Sci. 2011;56:145-50.
13. Wang X, Ling L, Li S, Qin G, Cui W, Li X, et al. The diagnostic value of gastrin-17 detection in atrophic gastritis. Medicine. 2016; 95:e3599.
14. Rugge M, Correa P, Di Mario F, El-Omar E, Fiocca R, Geboes K, et al. OLGA staging for gastritis: a tutorial. Dig Liver Dis. 2008;40:650-8.
15. Lôbo MRA, Chaves DM, de Moura DTH, Ribeiro IB, Ikari E, de Moura EGH. Safety and efficacy of EUS-guided coil plus cyanoacrylate versus conventional cyanoacrylate technique in the treatment of gastric varices: a randomized controlled trial. Arq Gastroenterol. 2019;56:99-105.
16. Malfertheiner P, Megraud F, O'Morain CA, Gisbert JP, Kuipers EJ, Axon AT, et al. Management of *Helicobacter pylori* infection- The Maastricht IV/Florence Consensus Report. Gut. 2012;61:646-64.
17. Dixon MF, Genta RM, Yardley JH, Correa P. Classification and grading of gastritis. The updated Sydney System. International Workshop on the histopathology of gastritis, Houston 1994. Am J Surg Pathol. 1996;20:1161-81.

18. Mc Nicholl AG, Forné M, Barrio J, De la Coba C, Gonzalez B, Rivera R, et al. Accuracy of GastroPanel for the diagnosis of atrophic gastritis. Eur J Gastroenterol Hepatol. 2014;26:941-8.
19. Bossuyt PM, Reitsma JB, Bruns DE, Gatsonis CA, Glasziou PP, Irwig L, et al. STARD 2015: an updated list of essential items for reporting diagnostic accuracy studies. Clin Chem. 2015;61:1446-52.
20. Zullo A. Follow-up of intestinal metaplasia in the stomach: When, how and why. World J Gastrointest Oncol. 2012;4:30-6.
21. Weck MN, Brenner H. Prevalence of chronic atrophic gastritis in different parts of the world. Cancer Epidemiol Biomarkers Prev. 2006;15:1083-94.
22. Marques SB, Mattar R, Artifon EL, Sakai P, Carrilho FJ. High prevalence of duodenal ulcer in a tertiary care hospital in the city of São Paulo, SP, Brazil. Arq Gastroenterol. 2011;48:171-4.
23. Lars Agréus TS, Aro P, Ronkainen J, Talley NJ, Sipponen P. Clinical use of proton-pump inhibitors but not H2-blockers or antacid/alginates raises the serum levels of amidated gastrin-17, pepsinogen I and pepsinogen II in a random adult population. Scand J Gastroenterol. 2009;44:564-70.
24. Feldman M, Richardson CT, Walsh JH. Sex-related differences in gastrin release and parietal cell sensitivity to gastrin in healthy human beings. J Clin Invest. 1983;71:715-20.
25. Bellolio E, Riquelme I, Riffo-Campos AL, Rueda C, Ferreccio C, Villaseca M, et al. Assessment of gastritis and gastric cancer risk in the Chilean population using the OLGA System. Pathol Oncol Res. 2019;25:1135.
26. Osumi H, Fujisaki J, Suganuma T, Horiuchi Y, Omae M, Yoshio T, et al. A significant increase in the pepsinogen I/II ratio is a reliable biomarker for successful *Helicobacter pylori* eradication. PLoS ONE. 2017;12:e0183980.

ORIGINAL ARTICLE

AG-2019-172
doi.org/10.1590/S0004-2803.202000000-30

Bowel frequency and symptoms of constipation and its relation with the level of physical activity in patients with Chagas disease

Daniela Carolina Barizon **TEZA**[1], Érika Cristina **FERREIRA**[1] and Mônica Lúcia **GOMES**[2]

Received: 11 December 2019
Accepted: 20 February 2020

ABSTRACT – **Background** – Intestinal constipation (IC) in patients with the digestive form of Chagas disease is one of the main reasons for seeking medical care. Population data indicate that the practice of physical activity improves gastrointestinal motility. **Objective** – This study evaluated the bowel frequency and symptoms of constipation and their relationship with the level of physical activity in patients with and without Chagas disease. **Methods** – Patients (n=120) of both genres, aged between 35 and 84 years, in which 50% (n=60) were in the Chagas group and 50% (n=60) were in the control group, were evaluated regarding the level of IC using the *Constipation Assessment Scale* (CAS) and regarding the level of physical activity using the International Physical Activity Questionnaire (IPAQ). **Results** – Patients in the Chagas group classified as active (IPAQ 2) had higher proportion (*P*=0.0235) of moderate IC with severe abdominal distension (*P*=0.0159) and decreased evacuation frequency (*P*=0.0281) than the patients in the control group, considered to be very active (IPAQ 1). The sedentary lifestyle was greater (*P*=0.0051) in the Chagas group with duration, intensity and frequency of physical activity lower than the control group. The health perception in the Chagas group was regular for 46.7% (*P*=0.0035) and poor for 8.3% (*P*=0.0244). **Conclusion** – There is a lower risk of developing intestinal constipation in more active individuals, evidencing that the level of physical activity interferes with bowel frequency and symptoms of constipation in patients with and without Chagas disease. The level of physical activity and health perception were worse in the Chagas group, reinforcing the disease stigma, which should be modified by the training of health professionals who routinely attend these patients.

HEADINGS – Chagas disease. *Trypanosoma cruz*i. Constipation. Exercise.

INTRODUCTION

Chagas disease is still a major public health problem, causing disability in infected individuals and more than 10,000 deaths per year[1]. Five to seven million people, mainly in Latin America, are infected with the protozoan *Trypanosoma cruzi*, the causative agent of this disease[1,2]. In Brazil, it was estimated in the year 2015 that a little more than 3 million individuals from the various Brazilian States are infected, predominantly in the Northeast, Central-west and Southeast regions[3].The migration of these individuals to non-endemic countries has made this disease a global health problem[4].

The digestive form of Chagas disease affects up to 10% of patients[5]. This form consists of dilation of the esophagus and colon due to neuronal destruction of the gastrointestinal tract and in the most severe cases causes malnutrition and chronic constipation[6]. This constipation has a slow and progressive evolution, starting with the difficulty of eliminating intestinal gases until the almost total impossibility for stool evacuation[6,7]. Intestinal constipation (IC) is one of the main reasons for seeking medical care, and the presence of complications in hospitalized patients increases the therapeutic costs for the public health system[7]. Population data indicate a lower frequency of constipation in individuals who practice more physical activity, as it improves gastrointestinal motility, with proportional alterations to the amount of activity practiced[8,9]. Studies involving these two variables related to preexisting diseases, such as Chagas disease, are necessary in order to propose interventions that minimize and control the problems related to the functional decline, and guide practices consistent with the reality of the population studied[4,5]. This requires practical, reliable, low-cost instruments with a considerable amount of information and easy application[10,11]. Questionnaires with an epidemiological approach and exploratory character are attractive[12]. In this context, the Constipation Assessment Scale (CAS)[11] can be used together with the International Physical Activity Questionnaire (IPAQ), proposed by the World Health Organization in 1998 and validated in twelve countries, including Brazil[12].Through these instruments, this study we evaluated the bowel frequency and symptoms of constipation and their relationship with the level of physical activity in patients with and without Chagas disease.

METHODS

Study population

A quantitative cross-sectional study was performed between July 2015 and July 2016 in two large municipalities, with population ranging from 300 to 600 thousand inhabitants, located in the North and Northwest regions of Paraná, Southern Brazil. The

Declared conflict of interest of all authors: none
Disclosure of funding: no funding received
[1] Universidade Estadual de Maringá, Centro de Ciências da Saúde, Programa de Pós-Graduação em Ciências da Saúde, Maringa, PR, Brasil. [2] Universidade Estadual de Maringá, Departamento de Ciências Básicas da Saúde, Parasitologia, Maringá, PR, Brasil.
Corresponding author: Mônica Lúcia Gomes. E-mail: monicaluciagomes@gmail.com

study population came from a spontaneous demand in the services where they were attended, consisting of 120 patients of both sexes, aged 35 to 85 years. Sixty patients without Chagas disease (control group) were treated at the outpatient clinic of the University Hospital of Maringá and 60 patients with clinical, laboratory diagnosis and the different clinical forms of Chagas disease (Chagas group) were treated by the Chagas Disease Laboratory of the Maringá State University (LDCh/UEM) and the Outpatient Clinic of the Northern Paraná Regional University Hospital – Londrina State University (HURNP/UEL). The patients were recruited through analysis and data collection from medical records and through individual interviews they were informed and invited to participate voluntarily in the study. Two questionnaires were applied to each patient, who signed the Free and Informed Consent Form, approved by the Ethics Committee in Research with Human Beings (COPEP) of the Maringá State University (registration 020938/2015) and by the Brazil Platform (Registration 43114115.9.0000.0104).

Variables studied

Bowel frequency and symptoms of constipation were assessed using the Constipation Assessment Scale (CAS), which identifies the presence and intensity of intestinal constipation. It consists of eight objective questions, involving the following themes: abdominal distension, alterations in gas elimination, lower frequency of evacuations, involuntary loss of liquid feces, full rectum or pressure sensation, rectal pain during evacuation, lower amount of feces elimination and desire and absence of evacuation. For each one of these themes, points were scored: zero (0) for no problem (absence of the symptom questioned), one (1) point for some problem (low intensity or frequency of the symptom) and two (2) points to severe problem (high intensity or frequency of the symptom). The sum of the scores resulted in the total score for each individual, in order to measure the presence and severity of IC. Thus, these values were arranged in strata, being as following: 0–3, without IC; 4–7, mild IC; 8–11, moderated IC; and 12–16, severe IC[11].The level of physical activity was evaluated using the International Physical Activity Questionnaire (IPAQ), short version, consisting of 8 open-ended questions about the time spent per week in different dimensions of physical activity (walking and physical exertion of moderate and vigorous intensity), and about physical inactivity (sitting position). The questions inquire about the frequency (days/week) and the time (minutes/day) spent for performing the activities. It is considered as vigorous the physical activity that requires great physical exertion and breathing much more intense than normal; and moderate, the physical activity that requires some physical effort and breathing a little more intense than normal. Thus, to assess the level of physical activity, the patients were classified in: I– Very Active or 1: ≥30 minutes/session of vigorous activity ≥5 days/week; and/or ≥20 minutes/session of vigorous activity ≥3 days/week added to ≥30 minutes/session of moderate activity or walking ≥5 days/week; II– Active or 2: ≥20 minutes/session of vigorous activity ≥3 days/week; and/or ≥30 minutes/session of moderate activity or walking ≥5 days/week; and/or ≥150 minutes/week of any of the activities together (vigorous + moderate + walking); III– Irregularly Active A or 3: 150 minutes/week or 5 days/week of any of the activities together (vigorous + moderate + walking); IV– Irregularly Active B or 4: the patient who did not achieved any of the criteria of the recommendation regarding frequency or duration of activity and V– Sedentary or 5: ≤10 minutes/week of any of the activities together (vigorous + moderate + walking)[12].

The sociodemographic characteristics (genre, marital status, age, smoking, alcoholism, workload and schooling), associated pathologies and health perception were also investigated.

Statistical analysis

The data obtained were entered into a spreadsheet of the software Microsoft Excel 2010 and were statistically analyzed using the Software Statistica 8.0. Means and standard deviations were evaluated for the quantitative variables, followed by the Mann-Whitney test for comparison of the groups Chagas and control. For the qualitative variables, in turn, we used double-entry frequency tables with percentage followed by the Z test. The level of significance adopted in the tests was 5%, that is, associations with $P<0.05$ were considered significant.

RESULTS

In both groups, the largest number of patients were female, married and aged between 50 and 64 years and reported no associated pathologies. In the Chagas group, there was a higher proportion of patients who do not work outside the home ($P=0.0070$), who had a basic level of education ($P=0.0282$) and the perception of health as regular ($P=0.0395$) or bad ($P=0.0244$). In the control group, the proportion of patients working up to 5 hours/day ($P=0.0198$) and having higher education ($P=0.0001$) was higher (TABLE 1).

The relationship between the level of physical activity and the degree of intestinal constipation identified that patients in the Chagas group classified as active (IPAQ 2) had a higher proportion of moderate intestinal constipation ($P=0.0235$) than control group patients who were very active (IPAQ 1) and had no intestinal constipation ($P=0.0019$) (TABLE 2).

Moderate intestinal constipation prevailed in patients from the Chagas group ($P=0.0244$) compared to the control group (TABLE 3). A higher proportion of Chagas group patients reported severe abdominal distension problem ($P=0.0159$) and lower bowel movement frequency ($P=0.0281$) and control group patients had no abdominal distension problem ($P=0.0183$) and inability to eliminate stool ($P=0.0174$) (TABLE 4).

The Chagas group presented a higher proportion of sedentary people ($P=0.0051$) and the control group of active individuals ($P=0.0282$) (TABLE 3). The intensity ($P=0.0001$) and the frequency of moderate physical activity ($P=0.0001$) and the duration of walking ($P=0.0013$) were significantly lower in the Chagas group (TABLE 5).

DISCUSSION

In the present study we investigated the bowel frequency and symptoms of constipation and their relationship with the level of physical activity in patients with and without Chagas disease and showed that intestinal constipation was more severe in the Chagas group, especially regarding abdominal distension and the frequency of intestinal movement. In this group the level of physical activity was lower compared to the control group, identifying a relationship between physical activity and bowel frequency and symptoms of constipation, that is, less active patients present greater impairment of intestinal frequency and functioning. The contemporary lifestyle, which predisposes to the limitation of physical activities (such as the use of remote control, computers, video games, television, elevator, etc.), and which contribute to the reduction of efforts in daily tasks, tend to decrease the frequency and functioning intestinal[13,14], especially with regard to pre-existing diseases such as Chagas disease.

TABLE 1. Distribution of Chagas and control groups according to the variables evaluated in the patients.

Variables	Groups				*P*
	Chagas (n=60)		Control (n=60)		
	n	%	n	%	
Genre					
Female	41	68.3	49	81.7	0.0901
Male	19	31.7	11	18.3	0.0901
Marital status					
Married	43	71.7	39	65.0	0.4317
Widower	5	8.3	12	20.0	0.0685
Divorced	8	13.3	5	8.3	0.3794
Single	4	6.7	4	6.7	0.9999
Age range					
35 to 49 years old	11	18.3	12	20.0	0.8133
50 to 64 years old	27	45.0	31	51.7	0.4642
65 years or older	22	36.7	17	28.3	0.3280
Smoker					
Yes	3	5.0	7	11.7	0.1872
No	40	66.7	47	78.3	0.1574
Former smoker	17	28.3	6	10.0	0.0121*
Ethylist					
No	59	98.3	60	100.0	0.3125
Former alcoholist	1	1.7	0	0.0	0.3125
Workload					
Don't work out	15	25.0	4	6.7	0.0070*
Up to 5 hours	6	10.0	16	26.7	0.0198*
6 to 8 hours	36	60.0	29	48.3	0.2009
9 hours or more	3	5.0	11	18.3	0.0250*
Schooling					
No schooling	5	8.3	3	5.0	0.4696
Elementary school	41	68.3	29	48.3	0.0282*
High school	12	20.0	9	15.0	0.4725
Higher education	2	3.3	19	31.7	0.0001*
Health perception					
Bad	5	8.3	0	0.0	0.0244*
Regular	28	46.7	17	28.3	0.0395*
Good	20	33.3	29	48.3	0.0972
Very good	1	1.7	6	10.0	0.0551
Great	6	10	8	13.3	0.5742

* Significant Z test considering 5% significance level.

TABLE 2. Relation between the level of intestinal constipation and level of physical activity of patients in groups Chagas and control.

CAS	IPAQ	Groups				*P*
		Chagas (n=60)		Control (n=60)		
		n	%	n	%	
Without IC	1	4	8.2	15	30.6	0.0019*
Without IC	2	23	46.9	20	40.8	0.5007
Without IC	3	5	10.2	4	8.2	0.7047
Without IC	4	9	18.4	5	10.2	0.1995
Without IC	5	2	4.1	5	10.2	0.1947
Total		43	87.8	49	100.0	–
Mild IC	1	2	4.1	1	2.0	0.5036
Mild IC	2	3	6.1	8	16.3	0.0765
Mild IC	3	1	2.0	0	0.0	0.2709
Mild IC	4	1	2.0	1	2.0	0.999
Mild IC	5	3	6.1	0	0.0	0.0520
Total		10	20.4	10	20.4	–
Moderate IC	1	0	0.0	0	0.0	0.9999
Moderate IC	2	4	8.2	0	0.0	0.0235*
Moderate IC	3	0	0.0	0	0.0	0.999
Moderate IC	4	1	2.0	1	0.0	0.2709
Moderate IC	5	0	0.0	0	0.0	0.9999
Total		5	10.2	0	0.0	–
Severe IC	1	1	2.0	0	0.0	0.2709
Severe IC	2	0	0.0	1	2.0	0.2709
Severe IC	4	0	0.0	0	0.0	0.9999
Severe IC	3	0	0.0	0	0.0	0.9999
Severe IC	5	1	2.0	0	0.0	0.2709
Total		2	4.1	1	2.0	–

* Significant Z test considering significance level of 5%. CAS: Constipation Assessment Scale; IPAQ: International Physical Activity Questionnaire. 1= very active; 2= active; 3= irregular A; 4= irregular B; 5= sedentary.

TABLE 3. Classification of the level of intestinal constipation and level of physical activity of the patients in groups Chagas and control.

Variables	Groups				*P*
	Chagas (n=60)		Control (n=60)		
	n	%	n	%	
CAS classification					
Without CI	43	71.7	50	83.3	0.1308
Mild IC	10	16.7	9	15.0	0.7992
Moderated IC	5	8.3	0	0.0	0.0244*
Severe IC	2	3.3	1	1.7	0.5756
IPAQ classification					
1- Very active	2	3.3	5	8.3	0.2437
2- Active	29	48.3	41	68.3	0.0282*
3- Irregular A	6	10.0	2	3.3	0.1434
4- Irregular B	11	18.3	10	16.7	0.8180
5- Sedentary	12	20.0	2	3.3	0.0051*

* Significant Z test considering significance level of 5%. IC: intestinal constipation; CAS: Constipation Assessment Scale; IPAQ: International Physical Activity Questionnaire.

TABLE 4. Distribution of the characteristics of the Constipation Assessment Scale (CAS) according to the variable intensity of intestinal constipation in the patients in groups Chagas and control.

Variables	Groups				*P*
	Chagas (n=60)		Control (n=60)		
	n	%	n	%	
Abdominal distension					
No problem	27	45.0	40	66.7	0.0183*
Some problem	23	38.3	18	30.0	0.339
Serious problem	10	16.7	2	3.3	0.0159*
Alteration in the amount of gas elimination					
No problem	36	60.0	45	75.0	0.0820
Some problem	18	30.0	13	21.7	0.3012
Serious problem	6	10.0	2	3.3	0.1434
Lower evacuation frequency					
No problem	41	68.3	43	71.7	0.6852
Some problem	10	16.7	15	25.0	0.2654
Serious problem	9	15.0	2	3.3	0.0281*
Loss of liquid feces					
No problem	49	81.7	56	93.3	0.0571
Some problem	7	11.7	3	5.0	0.1872
Serious problem	4	6.7	1	1.7	0.1748
Pressure or rectal repression sensation					
No problem	53	88.3	53	88.3	0.9999
Some problem	2	3.3	6	10.0	0.1434
Grave problem	5	8.3	1	1.7	0.0998
Rectal pain during evacuation					
No problem	52	86.7	52	86.7	0.9999
Some problem	3	5.0	7	11.7	0.1872
Serious problem	5	8.3	1	1.7	0.0998
Evacuation of low amount of feces					
No problem	45	75.0	53	88.3	0.0623
Some problem	11	18.3	6	10.0	0.1947
Serious problem	4	6.7	1	1.7	0.1748
Inability of eliminating feces					
No problem	52	86.7	59	98.3	0.0174*
Some problem	5	8.3	1	1.7	0.0998
Serious problem	3	5.0	0	0.0	0.0820

* There is a difference between the proportions by the Z test considering the level of significance of 5%.

Another result in the present study helping to evidence this relation between physical activity and bowel frequency and symptoms of constipation is the high percentage (46.9%) of individuals in Chagas group considered active (IPAQ 2) who did not have intestinal constipation. Researches indicate that individuals who practice more physical activity have a lower frequency of intestinal constipation[15], mainly due to the fact that physical activity improves gastrointestinal motility by stimulating peristalsis, improving pelvic and abdominal muscle tone, improving the intestinal pattern and consequently facilitating to expel the fecal bolus[16], that is, physical activity is such a protective factor against intestinal constipation[16,17]. Patients with Chagas disease are able and should perform physical activities, which, in addition to promoting improvements in cardiopulmonary function[17,18], may also improve the functioning of the gastrointestinal tract, according to the recommendations for management of intestinal constipation proposed by the American Association of Gastroenterology, which suggests the regular practice of physical activity[19,20].

Physical inactivity was more pronounced in the Chagas group. A randomized clinical trial showed that sedentary patients who maintained their lifestyle for 12 weeks had a higher degree of constipation and total colonic and rectosigmoid transit time than those who underwent regular physical training program for 12 weeks, confirming the influence beneficial of regular physical activity[20].

The duration, intensity and frequency of physical activity was shorter for patients in the Chagas group. The type, intensity and frequency of the activity performed significantly interfere with the response to infection[20,21]. The difference between the intensity of exercise performance is that moderate physical activity, even during infection, may not alter or improve the host immune response in both viral and parasitic infections[21,22]. In a study that a moderate intensity physical training program was applied in BALB/c mice, physical exercise was able to improve the body's response to *T. cruzi* infection, significantly reducing parasitemia peak and increasing survival[21].

In addition to the lower level of physical activity, the most severe constipation in the Chagas group may be related to the fact that *T. cruzi* infection promotes the destruction of enteric nervous system (SNE) nerve cells, and as a consequence, changes in the digestive system[22,23]. The SNE is located on the walls of the gastrointestinal tract and consists of about 100 million neurons, from

TABLE 5. Distribution of IPAQ variables - duration (D), intensity (I) and frequency (F) of physical activity in patients in groups Chagas and control.

Variables	Groups	n	Mean	±Standard deviation	Minimum	Maximum	*P*
Walking D (minutes)	Control	60	44.4	±24.3	0.0	90.0	0.0013*
	Chagas	60	29.6	±23.8	0.0	90.0	
Walking F (days)	Control	60	3.6	±2.2	0.0	7.0	0.0597
	Chagas	60	2.9	±2.3	0.0	7.0	
Moderate I D (minutes)	Control	60	45.3	±29.0	0.0	180.0	0.0001*
	Chagas	60	19.2	±22.3	0.0	90.0	
Moderate I F (days)	Controle	60	4.0	±2.5	0.0	7.0	0.0001*
	Chagas	60	2.2	±2.5	0.0	7.0	
Vigourus I D (minutes)	Controle	60	12.6	±21.8	0.0	60.0	0.0672
	Chagas	60	6.0	±16.0	0.0	60.0	
Vigourus I F (days)	Controle	60	0.8	±1.5	0.0	7.0	0.0542
	Chagas	60	0.3	±0.9	0.0	5.0	

* Significant Mann-Whitney test considering significance level of 5%; IPAQ: International Physical Activity Questionnaire.

the esophagus to the anus and has the function of integrating and coordinating the different visceral functions[24]. Auerbach's plexus is the structure most affected by the inflammatory process triggered by *T. cruzi* infection, as it is located in the viscera wall, causing a marked reduction in the number of nerve cells[25,26].

In the Chagas group, the number of more inactive individuals was higher, reaffirming the stigma of the disease (which has no cure, which can lead to death, especially if some physical effort, etc.)[27]. Another result of the present study that emphasizes this issue is that in the Chagas group a high percentage (55%) of patients rated their health as fair or poor when compared to the control group. In addition to undergoing a sudden change in their physical and mental health, the patient still suffers the repercussions of the disease in their life context[28]. The involvement of psychological aspects has been reported by several authors, emphasizing that the patient, upon learning about the disease, develops a reactive symptomatology, such as depression and anxiety[29,30]. This process is triggered by the hidden fear of malignant evolution and the impossibility of stopping the disease[29]. In this sense, the association of mental and psychic manifestations with Chagas disease, regardless of the clinical form presented, influence the evolution of the disease and the lives of patients[30].

In the Chagas group, the predominance of individuals with low educational level and who did not work outside the home or had lower workload, evidences the "weight" for patients who are carriers of a neglected disease that affects a less favored portion of society in addition to have fewer employment opportunities[31]. Other studies also demonstrated that the patients with Chagas disease have low educational level[32,33] and are mistakenly rejected when seeking employment, simply because they have a positive serology for *T. cruzi*, despite having the same work capacity as the individuals without Chagas disease[34,35]. Since it is a pathology of considerable social and economic impact, it is necessary to inform the population about the evolution of the disease, to train healthcare teams to instruct patients and to demystify the disease, stimulating the habitual practice of physical activity as an essential component for the establishment of an ideal health status[36,37].

The results in the present study allow us to conclude that: bowel frequency and symptoms of constipation of the patient with and without Chagas disease is related to the level of physical activity; the level of intestinal constipation was significantly more pronounced in patients with Chagas disease, because they presented a severe abdominal distension problem and reduced evacuation frequency, which can be prevented by instructions programs in primary health care; the patients with Chagas disease were more sedentary, since they had shorter duration, intensity and frequency of physical activity; these patients had lower educational level, lower workload outside the home and worse levels of health perception, reinforcing the level of the disease stigma, which should be modified by the training of healthcare professionals who routinely attend these patients.

Authors' contribution

Teza DCB: study concept and design, drafting the manuscript, data collect and drafting the manuscript. Gomes ML: critical revision of the manuscript for important intellectual content. Ferreira EC: statistical review of manuscript.

Orcid

Daniela Carolina Barizon Teza: 0000-0003-0733-206X.
Érika Cristina Ferreira: 0000-0002-1890-4943.
Mônica Lúcia Gomes: 0000-0001-5701-5375.

Teza DCB, Ferreira EC, Gomes ML. Frequência intestinal e sintomas de constipação e sua relação com o nível de atividade física em pacientes com doença de Chagas. Arq Gastroenterol. 2020;57(2):161-6.

RESUMO – **Contexto** – A constipação intestinal (CI) em pacientes com a forma digestiva da doença de Chagas é uma das principais razões para procura de atendimento médico. Os dados populacionais indicam que a prática de atividade física melhora a motilidade gastrointestinal. **Objetivo** – Este estudo avaliou a frequência intestinal e os sintomas de constipação e sua relação com o nível de atividade física em pacientes com e sem doença de Chagas. **Métodos** – Pacientes (n=120) de ambos os gêneros, com idades entre 35 e 84 anos, nos quais 50% (n=60) eram do grupo Chagas e 50% (n=60) do grupo controle, foram avaliados quanto ao nível da CI utilizando a Escala de Avaliação da Constipação (CAS) e o nível de atividade física utilizando o Questionário Internacional de Atividade Física (IPAQ). **Resultados** – Os pacientes do grupo Chagas classificados como ativos (IPAQ 2) apresentaram maior proporção (*P*=0,0235) de CI moderada com distensão abdominal grave (*P*=0,0159) e frequência de evacuação diminuída (*P*=0,0281) do que os pacientes do grupo controle, considerados muito ativos (IPAQ 1). O estilo de vida sedentário foi maior (*P*=0,0051) no grupo Chagas com duração, intensidade e frequência de atividade física menor que o grupo controle. A percepção de saúde no grupo Chagas foi regular para 46,7% (*P*=0,0035) e ruim para 8,3% (*P*=0,0244). **Conclusão** – Existe menor risco de desenvolver constipação intestinal em indivíduos mais ativos, evidenciando que o nível de atividade física interfere na frequência intestinal e nos sintomas de constipação em pacientes com e sem doença de Chagas. O nível de atividade física e percepção de saúde foram piores no grupo Chagas, reforçando o estigma da doença, que deve ser modificado pela capacitação dos profissionais de saúde que atendem rotineiramente esses pacientes.

DESCRITORES – Doença de Chagas. *Trypanosoma cruz*i. Constipação intestinal. Exercício físico.

REFERENCES

1. World Health Organization – WHO. Chagas disease in Latin America: an epidemiological update based on 2010 estimates. Wkly Epidemiol Rec 2015;90:33-44.
2. World Health Organization - WHO. Physical activity 2016. [Internet]. [Access 2017 January 20]. Available from: http://www.who.int/mediacentre/factsheets/fs385/en/.
3. Dias JCP, Ramos ANJ, Gontijo ED, Luquetti A, Shikanai-Yasuda MA, Coura JR, et al. II Consenso Brasileiro em Doença de Chagas 2015. Epidemiol Serv Saúde. 2016;25:7-86.
4. Schmunis GA, Yadon ZE. Chagas disease: a Latin American health problem becoming a world health problem. Acta Trop. 2010;115:14-21.
5. Centers For Disease Control And Prevention (CDC). Parasites - American Trypanosomiasis (also known as Chagas Disease): Epidemiology & Risk Factors 2013. [Internet]. [Access 2016 September 16]. Available from: http://www.cdc.gov/parasites/chagas/epi.html.
6. Santos JCMJ. Constipação Intestinal. Rev Bras Colo-proctol. 2005;5:79-93.
7. Gullo CE, Estofolete CF, Gil CD, Christiano AB. Digestive forms of Chagas disease and carcinogenesis: a study of association. Rev Col Bras Cir. 2012;39: 146-50.
8. Dukas L, Walter CW, Giovannucci EL. Association between physical activity, fiber intake, and other lifestyle variables and constipation in study of women. Am J Gastroenterology. 2003;98:1790-6.
9. Muller LSA, Kamm MA, Scarpignato C, Wald A. Myths and misconceptions about chronic constipation. Am J Gastroenterol. 2005;100:232-42.
10. Kohl HW, Craing CL, Lambert EV, Inoue S, Alkandari JR, Leetongin G, et al. The pandemic of physical inactivity: global action for public health. Lancet. 2012;21:294-305.
11. McMillan SC, Williams FA. Validity and reliability of the constipation assessment scale. Cancer Nurs.1989;12:183-8.
12. Matsudo S, Araújo T, Matsudo V, Andrade D, Andrade E, Oliveira LC, et al. Questionário Internacional de Atividade Física (IPAQ): estudo de validade e reprodutibilidade no Brasil. Rev Bras Ativ Fís Saúde. 2001;6:5-18.
13. Guedes DP, Lopes CC, Guedes, J. Reprodutibilidade e validade do Questionário Internacional de Atividade Física em adolescentes. Rev Bras Med Esporte. 2005;11:151-8.
14. Collete VL, Araújo CL, Magruga SW. Prevalência e fatores associados à constipação intestinal: um estudo de base populacional em Pelotas, Rio Grande do Sul, Brasil, 2007. Cad Saúde Pública. 2010;26:1391-402.
15. Simren M. Physical activity and the gastrointestinal tract. Eur J Gastroenterol Hepatol. 2002;14:1053-6.
16. Driessen LM, Jong JCK, Wijtzes A, Vries SI, Jaddoe VWV, Hofman A, et al. Physical activity and functional constipation during the preschool period: the generation R study. J Pediat Gastr Nutr. 2013;57:768-74.
17. Mendes MAF, Lopes WS, Nogueira GA, Wilson A, Araujo SM, Gomes ML. Exercício físico aeróbico em mulheres com doença de Chagas. Fisioter Mov. 2011;24:591-601.
18. Lopes WL, Ferreira EC, Silva SS, Tomiotto-Pellissier F, Costa IC, Pavanelli WR, et al. Physical training improves cardiopulmonary functional capacity and increases cytokine IL-10 levels in individuals with Chagas disease. Trop J Pharm Research. 2017;16:1319-26.
19. Locke GR, Pemberton JH, Phillips SF. AGA technical review on constipation. Gastroenterology. 2000;119:1766-78.
20. Schryver AM, Keulemans YC, Peters HP, Akkermans LM. Effects of regular physical activity on defecation pattern in middle-aged patients complaining of chronic constipation. Scand J Gastroenterol. 2005;40:422-9.
21. Schebeleski CS, Soares RCO, Moraes SMF, Dalalio MMO, Almeida FN, Toledo MJO, et al. Preinfection aerobic treadmill training improves resistance against *Trypanosoma cruzi* infection in mice. Appl Physiol Nutr Met. 2009;34:659-65.
22. Lowder T, Padgett DA, Woods JA. Moderate exercise early after influenza virus infection reduces the Th1 inflammatory response in lungs of mice. Exerc Immunol Rev. 2006;12:97-111.
23. Lowder T, Padgett DA, Woods JA. Moderate exercise protects mice from death due to influenza virus. Brain Behav Immun. 2005;19:377-80.
24. Guyton AC, Hall J. Tratado de Fisiologia Médica. 11 ed. Rio de Janeiro: Elsevier 2006.
25. Pinto JJ, Pinazo MJ, Saravia J, Gainsborg I, Magne HR, Cuatrecasas M, et al. Characterization of digestive disorders of patients with chronic Chagas disease in Cochabamba, Bolivia. Helion. 2019;5:120-6.
26. Guillén BP, Lugo AY, Moreno E. Dilatación del tracto digestivo de ratones infectados con *Trypanosoma cruzi*. Rev Invest Clínica. 2001;24:195-209.
27. Guariento ME, Camilo MVF, Camargo AMA. Situação trabalhista do portador de doença de Chagas crônica, em um grande centro urbano. Cad Saúde Pública. 1999;15:381-6.
28. Amato MS, Neto AV, Uip DE. Avaliação da qualidade de vida de pacientes com doença de Chagas submetidos a transplante de coração. Rev Soc Bras Med Trop. 1997;30:159-60.
29. Mota DCGA, Pereira AMTB, Gomes ML, Araújo SM. Estresse e resiliência em doença de Chagas. Aletheia. 2006;24:57-68.
30. Mangone CA, Sica REP, Pereyra S. Cognitive impairment in human chronic Chagas disease. Arq Neuropsiquiatr 1994;52:200-203.
31. Storino R, Auger S, Jörg M, Martino MS, Urrutia MI. Aspectos biológicos, psicológicos y sociales de la discriminación del paciente chagásico en Argentina. Rev Salud Pública. 2002;4:258-69.
32. Oliveira FAS, Bicalho GVC, Filho LDS, Silva MJ, Filho ZCG. Características epidemiológicas dos pacientes com doença de Chagas. Rev Bras Med Farmac Comun. 2006;2:107-13.
33. Gontijo ED, Rocha MOC, Oliveira UT. Perfil clínico-epidemiológico de chagásicos atendidos em ambulatório de referência de modelo de atenção ao chagásico na perspectiva do SUS. Rev Soc Bras Med Trop. 1996;29:101-8.
34. Dias JCP. Globalização, iniquidade e doença de Chagas. Cad Saúde Pública. 2007;23:13-22.
35. Ronan L, Souza LRMF, Freitas GL. Evolução de pacientes chagásicos acompanhados em um serviço de referência. Rev Soc Bras Med Trop. 2000;33:111-3.
36. Lopes WS, Cuman RKN, Guedes TA, Araujo SM, Gomes ML. Exercício aeróbio reduz a hipertensão arterial de mulheres com Doença de Chagas. Rev Bras Med Esporte. 2014;20:131-6.
37. Bielmann RM, Silva BGC, Coll CVN, Xavier MO, Silva SG. Impacto da inatividade física e custos de hospitalização por doenças crônicas. Rev Saúde Pública 2015;49:75-82.

ORIGINAL ARTICLE

AG-2019-174
doi.org/10.1590/S0004-2803.202000000-31

Molar incisor hypomineralization and celiac disease

Helen Helene **KUKLIK**, Izabela Taiatella Siqueira Alves **CRUZ**, Adriane **CELLI**, Fabian Calixto **FRAIZ** and Luciana Reichert da Silva **ASSUNÇÃO**

Received: 12 December 2019
Accepted: 6 February 2020

ABSTRACT – **Background** – Molar incisor hypomineralization (MIH) is a developmental enamel defect with multifactorial etiology. Although the relationship between celiac disease (CD) and developmental enamel defect was demonstrated, the association between CD and MIH is uncertain. **Objective** – The objective of this study was to analyze the occurrence of MIH in CD patients. **Methods** – Forty CD patients and a control group with 40 healthy individuals were selected. A calibrated examiner (k≥0.889) according to the European Academy of Pediatric Dentistry criteria performed the diagnosis of MIH. Data were analyzed by descriptive statistics and Fischer's exact test (α=0.05). **Results** – Of the 80 participants, ten presented MIH with eight individuals with CD. Celiac patients presented 4.75 times the chance of occurrence of MIH than the control group (95% CI: 2.22–10.18; *P*=0.044). In all the evaluated teeth (n=978), 22 had MIH: 20 teeth in individuals with CD and two in those without the disease. All CD participants with MIH presented the classic form of the disease. CD participants showed 17 teeth (85.0%) with demarcated opacities, two (10.0%) post-eruptive collapses and one (5.0%) atypical restoration. The control group presented only demarcated opacities. **Conclusion** – CD increased the chance of MIH and associated with its clinical manifestations can assist in the diagnosis of CD.

HEADINGS – Celiac disease. Tooth demineralization, etiology. Molar. Incisor. Permanent dentition.

INTRODUCTION

The molar incisor hypomineralization (MIH) is a type of qualitative enamel defect that affects the first permanent molars and may also be present in the incisors of the same dentition[1]. Clinically it is characterized by demarcated opacities of white, yellow or brown coloration and, in more severe cases, by the post-eruptive collapse of the enamel which may facilitate the development of dental caries and the increase of dental sensitivity[2].

The cause of MIH is still uncertain, and the studies suggest a multifactorial etiology associated with the defect, which may be of environmental or genetic origin[3,4]. Thus, because dental enamel cells are highly sensitive to external injuries, disturbances during the enamel maturation stage can lead to permanent defects in dental structures[4]. Systematic reviews have shown that complications during prenatal, perinatal and postnatal periods may be associated with MIH, including complications during pregnancy, low birth weight, respiratory diseases, recurrent fevers and the use of antibiotics in the first years of life[5-7]. Metabolic diseases and those that produce deficiencies in calcium and phosphate absorption are also associated with the onset of MIH[8,9].

Studies have shown that poor enamel formation may also be the result of hypocalcemia present in some diseases, such as celiac disease[10]. Celiac disease (CD) is an immune-mediated enteropathy induced by the ingestion of certain proteins (called gluten) in individuals of any age genetically predisposed. Gluten is the main protein component of wheat, barley, and rye, cereals that are widely consumed. Gluten sensitivity in celiac patients is due to an abnormal immune response responsible for villous atrophy in the small intestine, which is resolved by a gluten-free diet[11].

In addition to being the cause of nutritional deficiencies[12], poor intestinal absorption present in the CD development may also result in defects in the enamel[13]. A recent systematic review with meta-analysis concluded that individuals with celiac disease have a higher prevalence of developmental enamel defect (DED) when compared to individuals without the disease[14]. The association between DED and CD is still controversial and the triggering mechanisms of dental enamel defects in patients with celiac disease are still unknown. The poor enamel formation could be a consequence of the hypocalcemia resulting from this disease[10], of genetic predisposition[15] or an autoimmune reaction in the enamel organ during odontogenesis[16].

Although the relationship between DED and CD has been widely demonstrated, to our knowledge no study has investigated the association between MIH and CD. Thus, the objective of this study was to analyze the occurrence of MIH in Southern Brazilian patients with celiac disease compared to a control group without the disease.

METHODS

Ethical aspects

This research followed the parameters of the Declaration of Helsinki and was approved by the Human Ethics Committee of the Federal University of Paraná (process n. 41861015.0.0000.0102). The free and informed consent form was signed by all participants or their legal representatives.

Declared conflict of interest of all authors: none
Disclosure of funding: The authors report grants from *Coordenação de Aperfeiçoamento de Pessoal de Nível Superior* – Brasil (CAPES) – Finance code 001, during the conduct of the study.
Universidade Federal do Paraná, Curitiba, PR, Brasil.
Corresponding author: Luciana Reichert da Silva Assunção. E-mail: lurassuncao@yahoo.com.br

Study population

Forty patients with a celiac disease diagnosis were selected at the gastroenterology outpatient clinic of the Hospital de Clínicas of the Federal University of Paraná, Curitiba, Brazil. Another 40 participants without the disease, matched by age, and who attended the dental service of the Federal University of Paraná, Curitiba, Brazil, were also selected for this study.

For the group of patients with celiac disease, participants previously diagnosed through a positive anti-endomysial-antibody test (IgA) and a definitive confirmation of the disease through a small-bowel biopsy associated with positive serology for celiac disease were included. For the group of participants without celiac disease, patients who had no confirmed diagnosis for CD and who did not have gastrointestinal signs and symptoms were selected.

Participants who exhibited fluorosis, enamel development defects associated with other systemic diseases such as congenital porphyria, hemolytic anemias, and chronic renal failure, and those who used drugs that may have caused dentin pigmentation, such as tetracyclines, were excluded. Also excluded were patients who were using orthodontic braces at the time of examination.

Types of celiac disease

Celiac disease was classified according to the clinical signs and symptoms of the disease in the classic, nonclassical and asymptomatic. The classic form develops from the introduction of gluten protein in the diet, between 6 and 24 months of age and has gastrointestinal symptoms such as chronic diarrhea, anorexia, abdominal distension, abdominal pain, weight loss, and vomiting. Some patients with the classical form of the disease can still present severe malnutrition, leading to hypocalcemia. The non-classical form has extra intestinal symptoms, such as dermatitis herpetiformis, enamel hypoplasia in permanent teeth, osteoporosis, short stature, delayed puberty and iron deficiency anemia not responsive to oral treatments. The asymptomatic or silent form is characterized by histological changes in the intestinal mucosa and absence of clinical manifestations. It usually occurs among first-degree relatives of celiac patients[17].

Calibration

One of the study researchers (ITSAC) was previously calibrated for clinical identification of hypomineralization of molars and incisors, according to the criteria of the European Academy of Pediatric Dentistry (EAPD), which includes demarcated opacity, atypical restoration, post-eruptive fracture and extraction due to MIH[18].

The training and the calibration were performed in two stages, and in both, 30 photographs with different clinical situations of the MIH were used. The examiner's results were compared with a standard examiner (LRSA) with experience in this type of research. The data were statistically analyzed according to the calculation of the kappa coefficient for the evaluation of inter-examiner agreement (kappa =0.926). After one week, the same photographs were again evaluated by the examiner in training (duplicate examination) and statistically analyzed by the kappa coefficient for the evaluation of the intra-examiner agreement (kappa =0.889).

Clinical examination

The clinical examination was performed in a conventional chair and under natural light, using a flat mirror and a blunt tip, after cleaning the dental surfaces with sterile gauze. The criteria for a diagnosis of MIH followed the proposal of the European Academy of Pediatric Dentistry (EAPD), in which at least one first molar must have demarcated opacity (FIGURE 1.A), post-eruptive fracture (FIGURE 1.B), the presence of atypical restoration (FIGURE 1.C) or exodontia due to the condition[18]. The opacities were classified according to their coloration in white (FIGURE 2.A), yellow (FIGURE 2.B) or brown (FIGURE 2.C). The demarcated opacities were considered mild injuries, while post-eruptive fractures, atypical restorations, and MIH exodontia were considered severe[19]. Only defects greater than 1.0 mm in diameter were evaluated[20] and the differential diagnosis for white caries lesions was based on the criteria of Seow, 1997[4].

Statistical analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS – IBM Corp. Released 2017. IBM SPSS Statistics for Windows, version 25.0, Armonk, NY: IBM Corp.). The variables were analyzed in a descriptive way, through the absolute and relative frequencies. Fischer's exact test was used to verify the association between the presence of MIH and celiac disease. Odds ratio (OR) and its respective confidence intervals were also evaluated. The level of significance adopted for the analyzes was 5%.

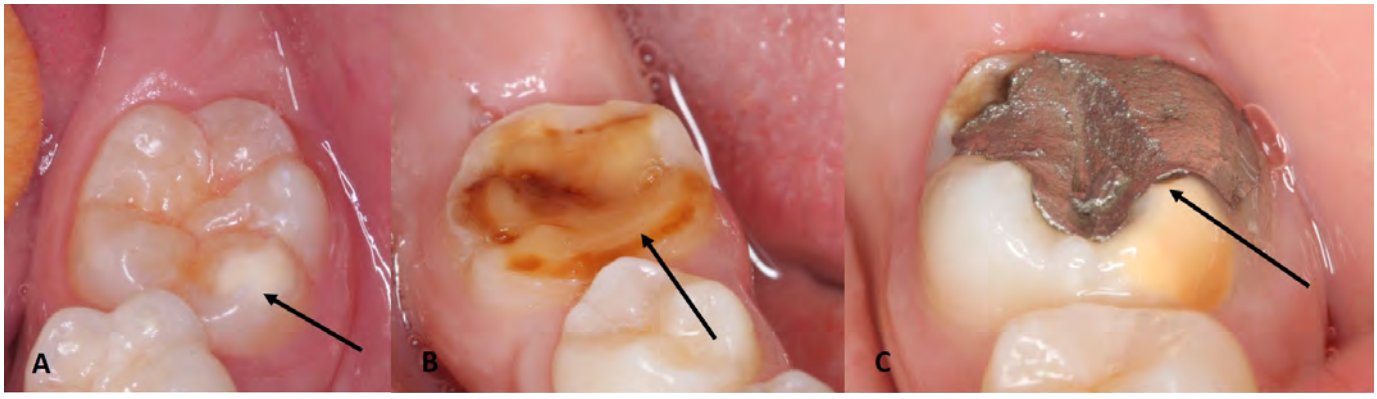


FIGURE 1. A. Demarcated opacity in a lower left first permanent molar (arrow). **B.** Post eruptive fracture in a lower right first permanent molar (arrow). **C.** Atypical restoration in a lower left first permanent molar (arrow).

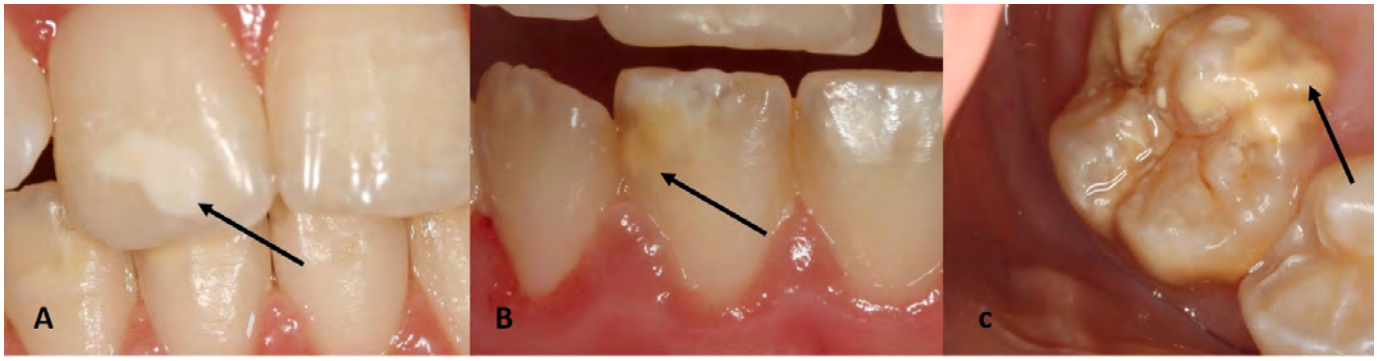


FIGURE 2. A. White demarcated opacity in an upper right permanent central incisor (arrow). **B.** Yellow demarcated opacity in a lower right permanent lateral incisor (arrow). **C.** Brown demarcated opacity in an upper right first permanent molar (arrow).

RESULTS

Of the 40 participants with CD, 29 (72.5%) were female, while of the 40 participants without CD, 28 (70.0%) were female. The groups showed a homogeneous distribution regarding sex (*P*=0.805). The median age of the participants was 16.50 and the minimum age was 5 years and a maximum of 34 years for both groups.

From the total of the participants, ten individuals presented the MIH (12.5%), being in eight individuals with CD (TABLE 1). There was a statistically significant association between MIH and DC, and individuals with the disease presented 4.75 times the chance of MIH occurrence when compared to participants without the disease (95% CI: 2.22–10.18; *P*=0.044).

TABLE 1. Occurrence of MIH according to the presence or absence of celiac disease (n=80).

MIH	Celiac disease		Total	*P**
	Yes	No	n (100%)	
	n (%)	n (%)		
Yes	8 (80.0)	2 (20.0)	10	
No	32 (45.7)	38 (54.3)	70	**0.044**
Total	40	40	80	

* Fisher's Exact Test. Significant value highlighted in bold.

Of the 40 participants with CD, 30 (75%) presented the classic form of the disease, seven (17.5%) the nonclassical form and three (7.5%) the asymptomatic. All participants with MIH were related to the manifestation of the classic form of the disease (TABLE 2).

TABLE 2. Distribution of MIH in relation to the type of celiac disease (n=40).

Type of celiac disease	MIH		Total
	Yes	No	
	n (%)	n (%)	
Classic	8 (73.3)	22 (26.7)	30
Nonclassical	0 (0)	7 (100)	7
Asymptomatic	0 (0)	3 (100)	3
Total	8	32	40

MIH: molar incisor hypomineralization.

In all teeth evaluated (n=978), 22 presented MIH, with 20 teeth present in individuals with CD and two among those without the disease. Of the 22 teeth with MIH, 19 (86.4%) were demarcated opacities, 2 (9.1%) post-eruptive collapse and 1 (4.5%) atypical restoration (FIGURE 3.A). Of the 20 teeth affected by MIH among participants with CD, 17 (85.0%) were demarcated opacities, 2 (10.0%) post-eruptive collapses and 1 (5.0%) atypical restoration (FIGURE 3.B). On the other hand, all (two teeth) affected by MIH among the participants without CD were demarcated opacities (FIGURE 3.C).

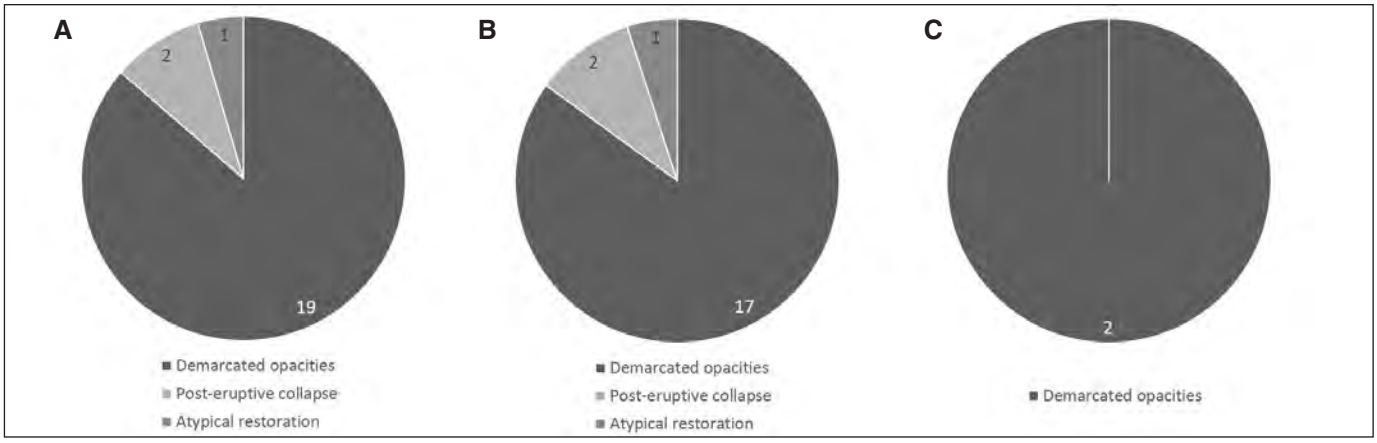


FIGURE 3. A. Distribution of the MIH type in the 22 affected teeth in the total of the participants with the change (n=10). **B.** Distribution of MIH type in the 20 affected teeth in participants with CD (n=8). **C.** Distribution of the MIH type in the 2 affected teeth in the participants without CD (n=2).

DISCUSSION

This study showed that the chance of occurrence of MIH is greater in individuals with celiac disease when compared to those without the disease. To our knowledge, no study evaluated the association of this specific type of DED with CD. A recent systematic review and meta-analysis observed a strong association considering both types DED and CD. In the selected studies, of the total of 2840 individuals with celiac disease approximately half had some type of DED[14]. A recent study in Brazil found a 138% greater chance of DED in patients with celiac disease, when compared to those without the disease[21]. In this sense, the North American Society of Pediatric Gastroenterology, Hepatology and Nutrition included DED as an important signal for the diagnosis of celiac disease[17], which shows that this oral condition can be an important tool for tracking the disease.

The classification used in most of the studies evaluating the presence of DED in participants with CD was the one proposed by AINE (1986)[22] in which it includes degrees of severity of the clinical aspect of the defect ranging from 0 to 4 (0 = no defect, 1 = defects in enamel coloring, 2 = slight structural defects, 3 = obvious structural defects, 4 = severe structural defects). In this classification, opacities without loss of structure, such as MIH, are included in category 1. Several studies have shown a higher prevalence of grade I defects in celiac patients[21,23-25].

The most observed form of celiac disease in the study was the classic one, in which the individuals presented mainly gastrointestinal symptoms, such as abdominal pain, diarrhea, vomiting, and abdominal distension. This subgroup of the disease has its manifestation from the introduction of gluten in the diet, at around six months to one year of age[26]. Among individuals with celiac disease, only those with the classic form of the disease had MIH. This is likely to occur because of the lower absorption of nutrients in the gastrointestinal tract in individuals with the classical form, which may result in hypocalcemia[27], which may render patients with low calcium levels more susceptible to defects of enamel[10].

The demarcated opacities were the types of MIH most frequent in the teeth evaluated in both the CD group and the disease (FIGURE 2). These findings corroborate the results found in a study conducted in Nepal[28] and in studies in Brazil as well[29,30]. A recent study showed a negative impact of MIH in the quality of life of schoolchildren with a predominance of demarcated opacities, showing that even injuries considered less severe should be incorporated into preventive and/or therapeutic strategies[29].

The most severe MIH lesions, i.e., post-eruptive collapse and atypical restoration, were present in only two participants (8 and 11 years old), both with CD (FIGURES 1.B and 1.C). Although this number can be considered without significance, this result can be justified due to a lower rate of calcium and phosphorus in the teeth of individuals with the disease when compared to those without the disease[25] making these teeth more brittle and less resistant to masticatory forces[31]. Further studies should be conducted to verify this association. To avoid the evolution of more serious consequences of MIH, such as the onset of caries lesions, topical applications of fluoride in opacities have been suggested, enabling the remineralization of impacted teeth[32].

The limitation of this study refers to its methodological design and sample size. Prevalence studies are limited in concluding a temporal relationship between exposure and outcome. Thus, longitudinal studies are indispensable to verify this association. In addition, larger sample searches are needed to increase the generalization of results.

The data from this study allow us to conclude that celiac disease increased the chance of molar incisor hypomineralization. The occurrence of MIH associated with other clinical manifestations may be an important tool in the diagnosis of the disease. In addition, the results show the importance of dental follow-up of individuals with CD, allowing preventive and/or therapeutic clinical actions to be performed in cases of MIH detection, avoiding more serious consequences such as post-eruptive fractures and even loss of the dental element.

Authors' contribution

Kuklik HH collected the data, interpreted data and wrote the manuscript. Cruz ITSA collected the data and contributed to the study design. Celli A contributed to the study design and performed the critical review of the manuscript. Fraiz FC contributed to the study design, interpretation of data and performed the critical review of the manuscript. Assunção LRS was the research adviser, contributed to the study design, statistical analysis, interpretation of data and performed the critical review of the manuscript.

Orcid

Helen Helene Kuklik: 0000-0003-0116-1335.
Izabela Taiatella Siqueira Alves Cruz: 0000-0003-4633-2871.
Adriane Celli: 0000-0002-4392-2721.
Fabian Calixto Fraiz: 0000-0001-5290-7905.
Luciana Reichert da Silva Assunção: 0000-0002-7380-8583.

Kuklik HH, Cruz ITSA, Celli A, Fraiz FC, Assunção LRS. Hipomineralização de molares e incisivos e doença celíaca. Arq Gastroenterol. 2020;57(2):161-71.

RESUMO – **Contexto** – A hipomineralização de molares e incisivos (HMI) é um defeito de desenvolvimento de esmalte com etiologia multifatorial. Embora a relação entre doença celíaca (DC) e defeito de desenvolvimento de esmalte já tenha sido demonstrada, a associação entre DC e HMI ainda é incerta. **Objetivo** – O objetivo deste estudo foi analisar a ocorrência de HMI em pacientes com DC. **Métodos** – Foram selecionados 40 pacientes com DC e um grupo controle com 40 indivíduos sem a doença. O diagnóstico da HMI foi realizado por examinador calibrado (k≥0,889) segundo critérios da Academia Europeia de Odontopediatria. Dados foram analisados por estatística descritiva e teste exato de Fischer (α=0,05). **Resultados** – Dos 80 participantes, 10 apresentaram HMI sendo 8 indivíduos com DC. Pacientes celíacos apresentaram 4,75 vezes a chance de ocorrência de HMI que grupo controle (IC 95%: 2,22–10,18; *P*=0,044). No total dos dentes avaliados (n=978), 22 apresentaram HMI: 20 dentes em indivíduos com DC e 2 entre aqueles sem a doença. Todos os participantes com DC e portadores de HMI apresentavam a forma clássica da doença. Participantes com DC mostraram 17 (85,0%) dentes com opacidades demarcadas, 2 (10,0%) colapsos pós-eruptivos e 1 (5,0%) restauração atípica. Grupo controle apresentou apenas opacidades demarcadas. **Conclusão** – DC aumentou a chance de HMI e associada a manifestações clínicas da DC pode auxiliar no diagnóstico da doença.

DESCRITORES – Doença celíaca. Desmineralização do dente, etiologia. Dente molar. Incisivo. Dentição permanente.

REFERENCES

1. Weerheijm KL, Jälevik B, Alaluusua S. Molar-Incisor Hypomineralisation. Caries Res 2001;35:390-1.
2. Americano GC, Jacobsen PE, Soviero VM, Haubek D. A systematic review on the association between molar incisor hypomineralization and dental caries. Int J Paediatr Dent. 2017;27:11-21.
3. Weerheijm, KL. Molar incisor hypomineralization (MIH): clinical presentation, aetiology and management. Dent Update. 2004;31:9-12.
4. Seow WK. Clinical diagnosis of enamel defects; pitfalls and practical guidelines. Int Med J 1997;47:173-82.
5. Alaluusua S. Aetiology of Molar-Incisor Hypomineralisation: A systematic review. Eur Arch Paediatr Dent. 2010;11:53-8.
6. Serna C, Vicente A, Finke C, Ortiz AJ. Drugs related to the etiology of molar incisor hypomineralization: A systematic review. J Am Dent Assoc. 2016;147:120-30.
7. Silva MJ, Scurrah KJ, Craig JM, Manton DJ, Kilpatrick N. Etiology of molar incisor hypomineralization - A systematic review. Community Dent Oral Epidemiol. 2016;44:342-53.
8. Johnson D, Kreji C, Hack M, Fanaroff A. Distribution of enamel defects and the association with respiratory distress in very low birth weight infants. J Dent Res. 1984;63:59-64.
9. Beentjes VEMV, Weerheijm KL, Groen HJ. Factors involved in the aetiology of Molar-Incisor Hypomineralisation (MIH). Eur J Paediatr Dent. 2002;1:9-13.
10. Nikiforuk G, Fraser D. The etiology of enamel hypoplasia: a unifying concept. J Pediatr. 1981;98:888-93.
11. Garnier-Lengliné H, Cerf-Bensussan N, Ruemmele FM. Celiac disease in children. Clin Res Hepatol Gastroenterol. 2015;39:544-51.
12. Rashid M, Zarkadas M, Anca A, Limeback H. Oral manifestations of celiac disease: a clinical guide for dentists. J Mich Dent Assoc. 2011;93:42-6.
13. Biçak DA, Urganci N, Akyüz S, et al. Clinical evaluation of dental defects and oral findings in coeliac children. Eur Oral Res. 2018;52:150-6.
14. Souto-Souza D, da Consolação Soares ME, Rezende VS, de Lacerda Dantas PC, Galvão EL, Falci SGM. Association between developmental defects of enamel and celiac disease: a meta-analysis. Arch Oral Biol. 2018;87:180-90.
15. Huarte M. A lncRNA links genomic variation with celiac disease. Science 2016;352:43-4.
16. Pastore L, Carroccio A, Compilato D, Panzarella V, Serpico R, Lo Muzio L. Oral manifestations of celiac disease. J Clin Gastroenterol. 2008;42:224-32.
17. Hill ID, Dirks MH, Liptak GS, Colletti RB, Fasano A, Guandalini S, et al. North American Society for Pediatric Gastroenterology, Hepatology and Nutrition. Guideline for the diagnosis and treatment of celiac disease in children: recommendations of the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition. J Pediatr Gastro-enterol Nutr. 2005;40:1-19.
18. Weerheijm KL, Duggal M, Mejàre I, Papagiannoulis L, Koch G, Martens LC, Hallonsten AL. Judgement criteria for molar incisor hypomineralisation (MIH) in epidemiologic studies: a summary of the european meeting on MIH held in Athens. Eur J Paediatr Dent. 2003;4:110-3.
19. Jeremias F, de Souza JF, Silva CM, Cordeiro Rde C, Zuanon AC, Santos-Pinto L. Dental caries experience and molar-incisor hypomineralization. Acta Odontol Scand. 2013;71:870-6.
20. Lygidakis NA, Wong F, Jälevik B, Vierrou AM, Alaluusua S, Espelid I. Best Clinical Practice Guidance for clinicians dealing with children presenting with Molar-Incisor-Hypomineralisation (MIH): An EAPD Policy Document. Eur Arch Paediatr Dent. 2010;11:75-81.
21. Cruz ITSA, Fraiz FC, Celli A, Amenabar JM, Assunção LR. Dental and oral manifestations of celiac disease. Med Oral Patol Oral Cir Bucal. 2018;23: 639-45.
22. Aine L. Dental enamel defects and dental maturity in children and adolescents with coeliac disease. Proc Finn Dent Soc 1986;82:71.
23. Avsar A, Kalayci AG. The presence and distribution of dental enamel defects and caries in children with celiac disease. Turk J Pediatr. 2008;50:45-50.
24. Trotta L, Biagi F, Bianchi PI, Marchese A, Vattiato C, Balduzzi D, et al. Dental enamel defects in adult celiac disease: prevalence and correlation with symptoms and age at diagnosis. Eur J Intern Med. 2013;24:832-34.
25. de Carvalho FK, de Queiroz AM, Bezerra da Silva RA, Sawamura R, Bachmann L, Bezerra da Silva LA, Nelson-Filho P. Oral aspects in celiac disease children: clinical and dental enamel chemical evaluation. Oral Surg Oral Med Oral Pathol Oral Radiol. 2015;119:636-43.
26. Krzywicka B, Herman K, Kowalczyk-Zajac M, Pytrus T. Celiac Disease and Its Impact on the Oral Health Status – Review of the literature. Adv Clin Exp Med. 2014;23:675-81.
27. Rabelink NM, Westgeest HM, Bravenboer N, Jacobs MA, Lips P. Bone pain and extremely low bone mineral density due to severe vitamin D deficiency in celiac disease. Arch Osteoporos. 2011;6:209-213.
28. Shrestha R, Upadhaya S, Bajracharya M. Prevalence of molar incisor hypomineralisation among school children in Kavre. Kathmandu Univ Med J. 2014; 2:38-42.
29. Portella PD, Menoncin BLV, de Souza JF, de Menezes JVNB1, Fraiz FC1, Assunção LRDS. Impact of molar incisor hypomineralization on quality of life in children with early mixed dentition: a hierarchical approach. Int J Paediatr Dent. 2019;1-11.
30. Raposo F, de Carvalho Rodrigues AC, Lia ÉN, Leal SC. Prevalence of hypersensitivity in teeth affected by molar-incisor hypomineralization (MIH). Caries Res. 2019;24:1-7.
31. Fagrell TG, Lingström P, Olsson S, Steiniger F, Norén JG. Bacterial invasion of dentinal tubules beneath apparently intact but hypomineralized enamel in molar teeth with molar incisor hypomineralization. Int J Paediatr Dent. 2008; 18:333-40.
32. Biondi AM, Cortese SG, Babino L, Fridman DE. Comparison of mineral density in molar incisor hypomineralization applying fluoride varnishes and casein phosphopeptide amorphous calcium phosphate. Acta Odontol Latinoam. 2017;30:118-23.

ORIGINAL ARTICLE

AG-2019-176
doi.org/10.1590/S0004-2803.202000000-32

Survival of patients with colorectal cancer in a Cancer Center

Samuel **AGUIAR JUNIOR**[1], Max Moura de **OLIVEIRA**[2], Diego Rodrigues Mendonça e **SILVA**[2], Celso Abdon Lopes de **MELLO**[3], Vinicius Fernando **CALSAVARA**[2] and Maria Paula **CURADO**[2]

Received: 17 December 2019
Accepted: 27 January 2020

ABSTRACT – **Background** – Hospital-based studies recently have shown increases in colorectal cancer survival, and better survival for women, young people, and patients diagnosed at an early disease stage. **Objective** – To describe the overall survival and analyze the prognostic factors of patients treated for colorectal cancer at an oncology center. **Methods** – The analysis included patients diagnosed with colon and rectal adenocarcinoma between 2000 and 2013 and identified in the Hospital Cancer Registry at A.C.Camargo Cancer Center. Overall 5-year survival was estimated using the Kaplan-Meier method, and prognostic factors were evaluated in a Cox regression model. Hazard ratios (HR) are reported with 95% confidence intervals (CI). **Results** – Of 2,279 colorectal cancer cases analyzed, 58.4% were in the colon. The 5-year overall survival rate for colorectal cancer patients was 63.5% (65.6% and 60.6% for colonic and rectal malignancies, respectively). The risk of death was elevated for patients in the 50–74-year (HR=1.24, 95%CI =1.02–1.51) and ≥75-year (HR=3.02, 95%CI =2.42–3.78) age groups, for patients with rectal cancer (HR=1.37, 95%CI =1.11–1.69) and for those whose treatment was started >60 days after diagnosis (HR=1.22, 95%CI =1.04–1.43). The risk decreased for patients diagnosed in recent time periods (2005–2009 HR=0.76, 95%CI =0.63–0.91; 2010–2013 HR=0.69, 95%CI =0.57–0.83). **Conclusion** – Better survival of patients with colorectal cancer improves with early stage and started treatment within 60 days of diagnosis. Age over 70 years old was an independent factor predictive of a poor prognosis. The overall survival increased to all patients treated in the period 2000–2004 to 2010–2013.

HEADINGS – Survival analysis. Colorectal neoplasms. Registries. Prognosis.

INTRODUCTION

In 2018, colorectal cancer (CRC) was the third most common cancer among men and the second most among women worldwide. It is the fourth cause of death from cancer among men and the second among women[1]. In Brazil, the estimates for 2018 show that CRC was the third most common cancer in men (17,380 cases; 8.7%) and the second in women (18,980 cases; 9.4%)[2].

Cancer incidence and mortality rate have been related to the human development of the countries. CRC incidence and mortality rates have been increasing in low- and middle-income countries, while it is stable or decreasing in highly developed countries[3]. Within Brazil, mortality rates and trends have been found to differ across federal units, after adjusting for socioeconomic conditions[4-5].

In terms of relative population survival, data from 296 registers show high variability in relative survival among patients with colon cancer. Israel, South Korea, and Australia have survival rates over 70%. The survival rate from six population-based cancer registries of Brazilian have been stable in fifteen years period (44.5% for 2000–2004, 50.6% for 2005–2009, and 48.3% for 2010–2014). For rectal cancer, relative survival has been more variable across world regions (294 registers), with only Korea and Australia having rates above 70%. In Brazil, the relative survival was 37.7% for 2000–2004, 45.7% for 2005–2009, and 42.4% for 2010–2014[6]. Hospital-based studies recently have shown increases in survival, and better survival for women, young people, and patients diagnosed at an early disease stage[7-10].

The survival data for patients treated at specialized cancer centers serves as an indicator of how a patient comes to be treated. Very few studies have use data from Brazilian hospital cancer registries to evaluate CRC survival. Thus, the objective this study was to describe the profile of patients treated for CRC at an oncology center and to analyze their survival.

METHODS

We included patients with CRC during the period of 2000 to 2013 who were treated at A.C.Camargo Cancer Center (ACCCC) with follow-up through December 31, 2018: invasive adenocarcinomas (M81403, 82013, 82103, 82113, 82203, 82613, 82623, 82633, 84413, 84703, 84803, 84813, 84903, 85103, 85603); colon cancer (ICD-O3 C18-19); and rectal cancer (ICD-O3 C20). We obtained the cases from the ACCCC's Hospital Cancer Registry. The ACCCC's Research Ethics Committee approved the project (n. 2462/17) on May 12, 2017.

Analyses were performed based on patient age group (≤49, 50–74, and ≥75 years of age), gender (male and female), period of

Declared conflict of interest of all authors: none
Disclosure of funding: no funding received
[1] Departamento de Cirurgia Pélvica, A.C.Camargo Cancer Center, São Paulo, SP, Brasil. [2] Grupo de Epidemiologia e Estatística em Câncer, Centro Internacional de Pesquisa, A.C.Camargo Cancer Center, São Paulo, SP, Brasil. [3] Departamento de Oncologia Clínica, A.C.Camargo Cancer Center, São Paulo, SP, Brasil.
Corresponding author: Maria Paula Curado. E-mail: mp.curado@accamargo.org.br

diagnosis (2000–2004, 2005–2009, and 2010–2013), site (left colon, right colon, unspecified, and rectal), clinical stage (I, II, III, and IV); delay to start treatment from the date of diagnosis in days (≤60 days and ≥61 days)[11]; type of treatment for the colon (surgery, surgery + chemotherapy, other combination, or none for the colon; surgery; surgery + chemotherapy, radiation therapy + chemotherapy; surgery + chemotherapy, + radiotherapy, other combination, or none for the rectal). Absolute and relative frequencies were calculated. Patients groups were compared with chi-squared tests.

Overall Survival (OS) was calculated as the difference between the date of diagnosis and the date of death (from any cause) or the date of the most recent information in the medical records. Survival curves were estimated by the Kaplan-Meier estimator, and 60-month probabilities were presented according to independent variables. Survival curves were compared with the log-rank test. Hazard ratios (HR) and associated 95% confidence intervals (95%CI) were estimated with a Cox regression model. The assumption of proportional hazards was assessed based on the so-called Schoenfeld residuals and the Grambsch and Therneau global test. There was one independent variable that did not satisfy the proportional hazards assumption (clinical stage) and thus the stratified Cox model by clinical stage was fitted. There was evidence that covariates had a constant effect over time in all cases. The significance level was fixed at 5% for all tests and the analyses performed in Stata SE 15.

RESULTS

Between 2000 and 2013, 2,279 patients with CRC were treated at the ACCCC. The majority of these patients were male (51.3%); 50–74 years old (62.5%), with colon cancer (58.4%), clinical stage III/IV (52.8%), and started treatment within 60 days of diagnosis (70.4%) (all $P<0.05$) (TABLE 1). Among colon cancer patients, 43.2% had surgery alone and 40.8% had surgery and chemotherapy. Among rectal cancer patients, 41.5% had surgery, chemotherapy, and radiation therapy, and 20.7% had surgery alone (TABLE 2).

We observed a 5-year OS rate of 63.5% (FIGURE 1.A), without difference between men and women. Survival was higher in patients younger than 49 years old (70.0%) and worse in those over 75 years old, 43.8% ($P<0.001$). OS was better for the most recent period (2010–2013, 66.4%) than for prior time periods ($P<0.012$, FIGURE 1.C). Patients younger than 49 years old with stage I or II colon cancer had an OS of 100%, while rectal cancer for stage I was 89.8% and 88.0% for stage II (TABLE 3). In the adjusted model stratified by clinical stage, mortality risk increased with increasing age (50–74 years HR=1.24; and ≥75 years HR=3.02) and was high for those diagnosed with rectal cancer (HR=1.37) and for those who started treatment more than 60 days after diagnosis (HR=1.22). Mortality risk was lowest for the two most recent time periods (2005–2009, HR=0.76; and 2010–2013, HR=0.69) (TABLE 4).

TABLE 1. Characteristics of patients diagnosed with colorectal cancer and treated at A.C.Camargo Cancer Center, between 2000 and 2013.

Characteristic	Colon N=1,332 n (%)	Rectal N=947 n (%)	Total N=2,279 n (%)	*P*
Gender				
Male	642 (48.2)	528 (55.8)	1,170 (51.3)	<0.001
Female	690 (51.8)	419 (44.2)	1,109 (48.7)	
Age group (years)				
≤49	245 (18.4)	204 (21.5)	449 (19.7)	
50–74	842 (63.2)	582 (61.5)	1,424 (62.5)	0.160
≥75	245 (18.4)	161 (17.0)	406 (17.8)	
Period of diagnosis				
2000–2004	233 (17.5)	202 (21.3)	435 (19.1)	
2005–2009	413 (31.0)	355 (37.5)	768 (33.7)	<0.001
2010–2013	686 (51.5)	390 (41.2)	1,076 (47.2)	
Site				
Right colon	-	-	377 (16.5)	
Left colon	-	-	819 (35.9)	
Colon (non-specified)	-	-	136 (6.0)	-
Rectal	-	-	947 (41.6)	
Clinical stage				
I	264 (19.8)	163 (17.2)	427 (18.7)	
II	318 (23.9)	216 (22.8)	534 (23.4)	
III	318 (23.9)	313 (33.1)	631 (27.7)	<0.001
IV	380 (28.5)	192 (20.3)	572 (25.1)	
No data	52 (3.9)	63 (6.6)	115 (5.1)	
Delay to start treatment				
≤60 days	1,003 (78.5)	546 (59.1)	1.549 (70.4)	<0.001
≥61 days	274 (21.5)	378 (40.9)	652 (29.6)	

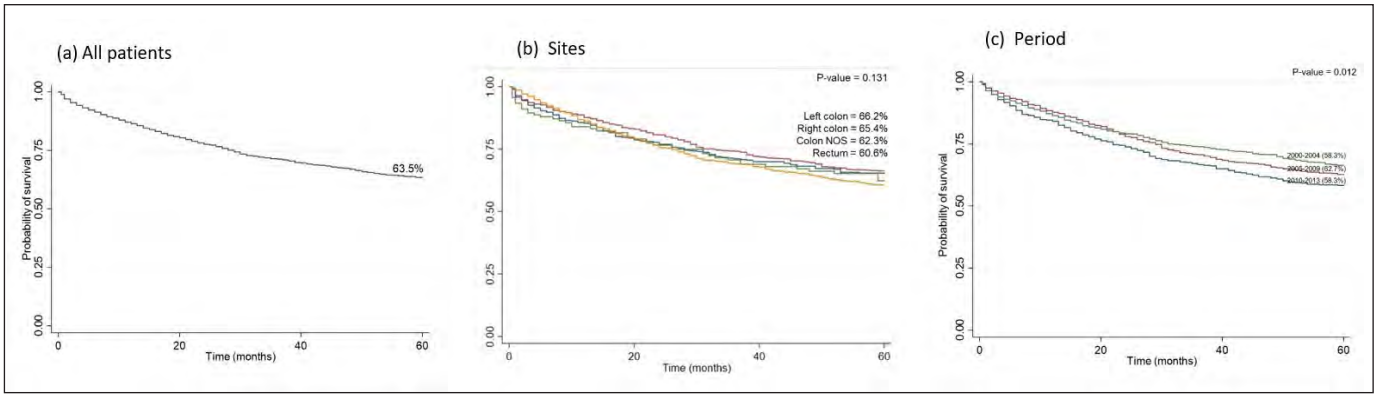


FIGURE 1. Kaplan-Meier 5-year overall survival rates for patients with colorectal cancer from 2000 to 2013.

TABLE 2. Treatments to colorectal cancer patients, by clinical stage, at A.C.Camargo Cancer Center, between 2000 and 2013.

Treatment	I	II	III	IV	Total
Colon					
Surgery	247 (93.6)	202 (63.5)	59 (18.6)	45 (11.8)	575 (43.2)
Surgery + CT	12 (4.6)	103 (32.4)	230 (72.3)	197 (51.8)	544 (40.8)
CT	0 (0)	1 (0.3)	8 (2.5)	73 (19.2)	84 (6.3)
Other(s)	4 (1.5)	8 (2.5)	20 (6.3)	37 (9.7)	71 (5.3)
None	1 (0.3)	4 (1.3)	1 (0.3)	28 (7.5)	58 (4.4)
All treatment groups	264 (100.0)	318 (100.0)	318 (100.0)	380 (100.0)	1.332 (100.0)
Rectal					
Surgery	99 (60.7)	41 (19.0)	31 (9.9)	15 (7.8)	196 (20.7)
Surgery + CT	1 (0.6)	24 (11.1)	70 (22.4)	49 (25.5)	147 (15.5)
Radiotherapy + CT	3 (1.8)	19 (8.8)	22 (7.0)	36 (18.8)	88 (9.3)
Surgery + RT + CT	48 (29.5)	114 (52.8)	178 (56.9)	40 (20.8)	393 (41.5)
CT	0 (0)	1 (0.5)	2 (0.6)	34 (17.7)	37 (3.9)
Other(s)	11 (6.8)	15 (6.9)	10 (3.2)	9 (4.7)	64 (6.8)
None	1 (0.6)	2 (0.9)	0 (0)	9 (4.7)	22 (2.3)
All treatment groups	163 (100.0)	216 (100.0)	313 (100.0)	192 (100.0)	947 (100.0)

CT: chemotherapy; RT: radiotherapy.

TABLE 3. Overall Survival for patients with colorectal cancer, according to characteristics and site, at A.C.Camargo Cancer Center between 2000 and 2013.

Characteristic	Colon			Rectal			All		
	Deaths/total	5-year OS	*P*	Deaths/total	5-year OS	*P*	Deaths/total	5-year OS	*P*
Gender									
Male	206/642	65.9	0.919	198/528	61.1	0.587	404/1,170	63.7	0.802
Female	226/690	65.3		362/419	59.9		390/1,109	63.2	
Age group (years)									
≤49	60/245	73.5		67/204	66.0		127/449	70.0	
50–74	246/842	69.1	<0.001	204/582	63.9	<0.001	450/1,424	66.9	<0.001
≥75	126/245	45.3		91/161	41.7		217/406	43.8	
Period of diagnosis									
2000–2004	92/233	60.4		89/202	55.9		181/435	58.3	
2005–2009	144/413	65.0	0.109	141/355	60.1	0.153	285/768	62.7	0.012
2010–2013	196/686	67.9		132/390	63.8		328/1,076	66.4	
Clinical staging by age group									
≤49 years									
I	0/43	100.0		3/32	89.8		3/75	95.4	
II	0/52	100.0	<0.001	5/45	88.0	<0.001	5/97	94.3	<0.001
III	10/63	82.6		18/72	73.8		28/135	77.8	
IV	47/80	37.8		35/43	16.8		82/123	30.3	
50-74 years									
I	11/170	92.7		12/100	87.4		23/270	90.7	
II	18/196	90.4	<0.001	27/125	77.6	<0.001	45/321	85.4	<0.001
III	38/207	80.6		60/206	70.1		98/413	75.3	
IV	162/241	28.0		94/121	20.3		256/362	25.3	
≥75 years									
I	17/51	64.2		8/31	70.3		25/82	66.5	
II	24/70	64.3	<0.001	21/46	54.2	<0.001	45/116	60.0	<0.001
III	24/48	43.6		19/35	43.9		43/83	43.4	
IV	47/59	17.5		26/28	7.1		73/87	14.1	
Starting treatment									
≤60 days	289/1,003	69.3	0.151	200/546	62.1	0.676	489/1,549	66.7	0.058
≥61 days	92/274	64.2		144/378	60.8		236/652	62.2	
Total	432/1,332	65.6		362/947	60.6		794/2,279	63.5	

OS: overall survival.

TABLE 4. Prognostic factors associated with colorectal cancer, by site (A.C.Camargo Cancer Center, 2000–2013).

Characteristic	Colon		Rectal		All	
	HR (95%CI)	HRa* (95%CI)	HR (95%CI)	HRa* (95%CI)	HR (95%CI)	HRa* (95%CI)
Gender						
Male	Reference	Reference	Reference	Reference	Reference	Reference
Female	1.01 (0.84; 1.22)	0.98 (0.81; 1.18)	1.06 (0.86; 1.30)	1.17 (0.95; 1.45)	1.02 (0.89; 1.17)	1.06 (0.92; 1.22)
Age group (yrs)						
≤49	Reference	Reference	Reference	Reference	Reference	Reference
50–74	1.24 (0.94; 1.65)	1.48 (1.11; 1.96)	1.09 (0.82; 1.43)	1.03 (0.78; 1.36)	1.15 (0.95; 1.40)	1.24 (1.02; 1.51)
≥75	2.85 (2.10; 3.88)	3.67 (2.69; 5.01)	2.27 (1.65; 3.11)	2.47 (1.80; 3.41)	2.54 (2.04; 3.16)	3.02 (2.42; 3.78)
Period of diagnosis						
2000–2004	Reference	Reference	Reference	Reference	Reference	Reference
2005–2009	0.87 (0.67; 1.12)	0.64 (0.49; 0.83)	0.83 (0.64; 1.08)	0.85 (0.65; 1.11)	0.85 (0.71; 1.03)	0.76 (0.63; 0.91)
2010–2013	0.77 (0.60; 0.99)	0.60 (0.47; 0.77)	0.77 (0.59; 1.01)	0.76 (0.58; 1.00)	0.76 (0.64; 0.91)	0.69 (0.57; 0.83)
Site						
Right colon	-	-	-	-	Reference	Reference
Left colon	-	-	-	-	0.94 (0.76; 1.17)	1.04 (0.84; 1.29)
Colon, NOS	-	-	-	-	1.10 (0.79; 1.55)	1.10 (0.79; 1.55)
Rectal	-	-	-	-	1.13 (0.92; 1.39)	1.37 (1.11; 1.69)
Starting treatment						
≤60 days	Reference	Reference	Reference	Reference	Reference	Reference
≥61 days	1.19 (0.94; 1.50)	1.19 (0.94; 1.51)	1.05 (0.84; 1.30)	1.22 (0.99; 1.53)	1.16 (0.99; 1.36)	1.22 (1.04; 1.43)

* Stratified by clinical stage; test of proportional-hazard assumption: colon (P=0.156); rectal (P=0.329); all (P=0.149).

Patients whose cancer was in the colon had a 5-year OS of 65.6%, (P<0.001). Subgroups of colon cancer patients with higher OS rates included patients who were ≤49 years old (73.5%) (TABLE 3). Mortality risk increased with increasing age (50–74 years HR=1.24; and ≥75 years HR=2.85). Mortality risk decreased for the most recent time periods (2005-2009 HR=0.87; and 2010–2013 HR=0.77) (TABLE 4).

Patients with rectal cancer had a 5-year OS rate of 60.6% (FIGURE 1.B). Again, subgroups of rectal cancer patients with higher OS rates included patients who were ≤49 years old (66.0%) (P<0.001) (TABLE 3). Mortality risk was increased among patients aged 75 and over (HR=2.47) (TABLE 4).

The best survival rates were observed among the subgroup of young patients with early stage (I–II) colon cancer, whose 5-year OS achieved 100%. The worst survival rates were observed among the subgroup of elderly patients with metastatic rectal cancer, whose 5-year OS were 7.1%.

DISCUSSION

The 5-year OS rate obtained for our CRC patient cohort (63.5%) was similar to those found in hospital-based studies in Iran (58.5% for 2005–2010)[12], Australia (63.0% for 2005–2010)[13], and Taiwan (68.7% for 2007–2013)[14], but notably higher than rates reported in China (range, 28.4–41.7% in the period of 2002–2014)[15]. We did not identify differences based on sex, even after adjusting for other characteristics[12-13]. Some studies have suggested that survival may be lower for men, due to differences in access to health services[7,16].

Survival decreased with increasing age, as previously described[7,12,16]. More than 80% of the patients were 50 years old or older. Increased age is a predictive factor for death in cancer patients[10,17] and has been associated with a higher risk of comorbidities, which reduce patient survival[18,19]. In a study in Japan, 20% of 792 patients had a Charlson Comorbidity Index (CCI) higher than or equal to 1, with a 1.20 increment of risk of overall mortality for each CCI point[10]. Meanwhile, in a Danish study of patients 70 years old or older, a 1.41 increase in the risk of overall mortality per CCI increment was observed[8]. These data reinforce the importance of the multidisciplinary team in treatment decision, as oncologic diagnosis is not the only risk.

We identified an improvement in survival in recent time periods. Similar results have previously been described[7,13,16]. Improved survival over time may be related to the implementation of treatment guidelines and new technologies to treat CRC.

OS was five percentage points higher for colon cancer patients (65.6%) than for rectal cancer patients (60.6%), consistent with prior studies reporting a poorer prognosis for rectal cancer than colon cancer[6,12-13,20]. In addition, our findings suggest that this lower of survival may be associated with the percentage of patients who began treatment more than 60 days after diagnosis (21.5% for colon cancer versus 40.9% for rectal cancer). As the treatment of rectal cancer is more complex than colon cancer, involving more exams for staging as well as the need of multimodality treatment, maybe these patients are more susceptible for delaying the start of treatment.

We did not identify any differences based on laterality of colon cancer (right vs left colon), contrasting with prior studies reporting lower survival rates for cancers located in the right colon[16,21,22]. In comparing survival rates across colon sites, we did not find differences in a combined analysis of patients with stage I, II, or III. However, we did identify a difference according to stage, in the right colon having a better prognosis when diagnosed at stage II (HR=0.92, 95%CI =0.87–0.97) than at stage III (HR=1.12, 95%CI =1.06–1.18)[16].

In terms of the type of treatment patients with stage I or II received only surgery, whereas patients with stage III or IV colon cancer received surgery combined with chemotherapy. For patients with rectal cancer stage II or III the treatment was surgery combined with both radiotherapy and chemotherapy. These findings were similar to those of other studies[13,23-25]. Advanced age may be an independent predictor to preclude adjuvant therapies[26].

Starting treatment more than 60 days after diagnosis was a predictor of poorer survival, which shows the need for implementing policies that enable universal access to early treatment[11].

Given than survival rates are better among patients in an early clinical stage, the CRC patient treated at the ACCCC had advanced-stage cancer (colorectal, 52-53%) underscores a need for the implementation of CRC screening programs[27-29]. It is notable that survival rates of patients with CRC showed an improvement over time. However, early stage remains critical and to ensuring that treatment starts as soon as possible following diagnosis.

Authors' contribution

Aguiar Junior S and Curado MP contributed to conception and design; Oliveira MM contributed to analysis, interpretation the data and drafted the manuscript; Silva DRM extracted the data and drafted the manuscript; Aguiar Junior S, Mello CAL, Calsavara VF critically reviewed the manuscript; Curado MP discussed, critically reviewed the manuscript and supervised the research. All authors approved the final version of the manuscript to be published.

Orcid

Samuel Aguiar Junior: 0000-0003-3476-727X.
Max Moura de Oliveira: 0000-0002-0804-5145.
Diego Rodrigues Mendonça e Silva: 0000-0001-8469-8415.
Celso Abdon Lopes de Mello: 0000-0002-8315-1562.
Vinicius Fernando Calsavara: 0000-0003-2332-5863.
Maria Paula Curado: 0000-0001-8172-2483.

Aguiar Junior S, Oliveira MM, Silva DRM, Mello CAL, Calsavara VF, Curado MP. Sobrevida de pacientes com câncer colorretal em um Cancer Center. Arq Gastroenterol. 2020;57(2):172-7.

RESUMO – **Contexto** – Estudos hospitalares recentes têm demonstrado aumento da sobrevida do câncer colorretal e melhor sobrevida para mulheres, jovens e pacientes diagnosticados em estágio precoce da doença. **Objetivo** – Descrever a sobrevida global e analisar os fatores prognósticos de pacientes tratados para câncer colorretal em um centro de oncologia. **Métodos** – Foram incluídos pacientes com diagnóstico de adenocarcinoma de cólon e reto entre 2000 e 2013, identificados no Registro Hospitalar de Câncer do A.C.Camargo Cancer Center. A sobrevida global aos 5 anos foi estimada pelo método de Kaplan-Meier e os fatores prognósticos foram avaliados pelo modelo de Cox. As razões de risco (HR) são relatadas com intervalos de confiança (IC) de 95%. **Resultados** – Dos 2.279 casos de câncer colorretal analisados, 58,4% eram de cólon. A taxa de sobrevida global aos 5 anos para pacientes com câncer colorretal foi de 63,5% (65,6% e 60,6% para câncer de cólon e retal, respectivamente). O risco de óbito foi elevado para pacientes na faixa etária de 50–74 anos (HR=1,24; IC95% =1,02–1,51) e ≥75 anos (HR=3,02; IC95% =2,42–3,78), para pacientes com câncer retal (HR=1,37; IC95% =1,11–1,69) e para aqueles cujo tratamento foi iniciado >60 dias após o diagnóstico (HR=1,22; IC95% =1,04–1,43). O risco diminuiu para pacientes diagnosticados em períodos recentes (2005–2009 HR=0,76; IC95% =0,63–0,91; 2010–2013 HR=0,69; IC95% =0,57–0,83). **Conclusão** – A sobrevida dos pacientes com câncer colorretal é maior naqueles em estágio inicial e com início do tratamento antes dos 60 dias.. Idade acima de 70 anos foi fator independente preditivo de mau prognóstico. A sobrevida global aumentou para todos os pacientes tratados no período de 2000–2004 a 2010–2013.

DESCRITORES – Análise de sobrevida. Neoplasias colorretais. Sistema de registros. Prognóstico.

REFERENCES

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68:394-424.
2. National Cancer Institute (INCA). Estimate 2018: Cancer incidence in Brazil. [Internet]. [Accessed 2019 June 19]. Available from: https://www.inca.gov.br/search/conteudo/estimativa
3. Arnold M, Sierra MS, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global patterns and trends in colorectal cancer incidence and mortality. Gut. 2017;66:683-691.
4. Guimaraes RM, Rocha PGM, Muzi CD, Ramos RS. Increase income and mortality of colorectal cancer in Brazil, 2001-2009. Arq Gastroenterol. 2013; 50:64-9.
5. Oliveira MM, Latorre MRDO, Tanaka LF, Rossi BM, Curado MP. Disparities in colorectal cancer mortality across Brazilian States. Rev Bras Epidemiol. 2018;21:e180012.
6. Allemani C, Matsuda T, Di Carlo V, Harewood R, Matz M, Nikšić M, et al.; CONCORD Working Group. Global surveillance of trends in cancer survival 2000-14 (CONCORD-3): analysis of individual records for 37 513 025 patients diagnosed with one of 18 cancers from 322 population-based registries in 71 countries. Lancet. 2018;391:1023-75.
7. Agüero F, Murta-Nascimento C, Gallén M, Andreu-García M, Pera M, Hernández C, et al. Colorectal cancer survival: results from a hospital-based cancer registry. Rev Esp Enferm Dig. 2012;104:572-7.
8. Jørgensen TL, Hallas J, Friis S, Herrstedt J. Comorbidity in elderly cancer patients in relation to overall and cancer-specific mortality. Br J Cancer. 2012;106:1353-60.
9. Quan D, Gallinger S, Nhan C, Auer RA, Biagi JJ, Fletcher GG, et al.; Surgical Oncology Program at Cancer Care Ontario. The role of liver resection for colorectal cancer metastases in an era of multimodality treatment: a systematic review. Surgery. 2012;151:860-70.
10. Morishima T, Matsumoto Y, Koeda N, Shimada H, Maruhama T, Matsuki D, et al. Impact of Comorbidities on Survival in Gastric, Colorectal, and Lung Cancer Patients. J Epidemiol. 2019;29:110-5.
11. Presidency of the Republic. Law 12.732/12 - Provides on the first treatment of patients with proven malignant neoplasia and establishes a deadline for its beginning. Official Journal of the Union 2012. Available at: https://www.planalto.gov.br/ccivil_03/_ato2011-2014/2012/lei/l12732.htm. Accessed on: May 10, 2019.
12. Zare-Bandamiri M, Khanjani N, Jahani Y, Mohammadianpanah M. Factors Affecting Survival in Patients with Colorectal Cancer in Shiraz, Iran. Asian Pac J Cancer Prev. 2016;17:159-63.
13. Roder D, Karapetis CS, Wattchow D, Moore J, Singhal N, Joshi R, et al. Colorectal cancer treatment and survival: the experience of major public hospitals in south Australia over three decades. Asian Pac J Cancer Prev. 2015;16:2431-40.
14. Lee CH, Cheng SC, Tung HY, Chang SC, Ching CY, Wu SF. The Risk Factors Affecting Survival in Colorectal Cancer in Taiwan. Iran J Public Health. 2018;47:519-30.
15. Chen JG, Chen HZ, Zhu J, Yang YL, Zhang YH, Huang PX, et al. Cancer survival in patients from a hospital-based cancer registry, China. J Cancer. 2018;9:851-60.
16. Weiss JM, Pfau PR, O'Connor ES, King J, LoConte N, Kennedy G, et al. Mortality by stage for right- versus left-sided colon cancer: analysis of surveillance, epidemiology, and end results--Medicare data. J Clin Oncol. 2011;29:4401-9.
17. Lee M, Cronin KA, Gail MH, Feuer EJ. Predicting the absolute risk of dying from colorectal cancer and from other causes using population-based cancer registry data. Stat Med. 2012;31:489-500.
18. Edwards BK, Noone AM, Mariotto AB, Simard EP, Boscoe FP, Henley SJ, et al. Annual Report to the Nation on the status of cancer, 1975-2010, featuring prevalence of comorbidity and impact on survival among persons with lung, colorectal, breast, or prostate cancer. Cancer. 2014;120:1290-314.
19. Yancik R, Ganz PA, Varricchio CG, Conley B. Perspectives on comorbidity and cancer in older patients: approaches to expand the knowledge base. J Clin Oncol. 2001;19:1147-51.
20. Yang J, Du XL, Li ST, Wang BY, Wu YY, Chen ZL, et al. Characteristics of Differently Located Colorectal Cancers Support Proximal and Distal Classification: A Population-Based Study of 57,847 Patients. PLoS One. 2016;11:e0167540.
21. Warschkow R, Sulz MC, Marti L, Warschkow R, Sulz MC, Marti L, et al. Better survival in right-sided versus left-sided stage I - III colon cancer patients. BMC Cancer. 2016;16:554.
22. Buchwald P, Hall C, Davidson C, Dixon L, Dobbs B, Robinson B, et al. Improved survival for rectal cancer compared to colon cancer: the four-cohort study. ANZ J Surg. 2018;88:E114-117.
23. Abu Hassan MR, Ismail I, Mohd Suan MA, Ahmad F, Wan Khazim WK, Othman Z, et al. Incidence and mortality rates of colorectal cancer in Malaysia. Epidemiol Health. 2016;38:e2016007.
24. Ghazali AK, Musa KI, Naing NN, Mahmood Z. Prognostic factors in patients with colorectal cancer at Hospital Universiti Sains Malaysia. Asian J Surg. 2010;33:127-133.
25. Yeole BB, Sunny L, Swaminathan R, Sankaranarayanan R, Parkin DM. Population-based survival from colorectal cancer in Mumbai, (Bombay) India. Eur J Cancer. 2001;37:1402-8.
26. Adelson P, Fusco K, Karapetis C, Wattchow D, Joshi R, Price T, Sharplin G, Roder D. Use of guideline-recommended adjuvant therapies and survival outcomes for people with colorectal cancer at tertiary referral hospitals in South Australia. J Eval Clin Pract. 2018;24:135-44.
27. Ghazali AK, Keegan TJ, Hassan MRA, Taylor BM. The effect of individual-level factors in survival prognosis for colorectal cancer in Malaysia. Int J Community Med Public Health. 2019;6:2313-20.
28. Lauby-Secretan B, Vilahur N, Bianchini F, Guha N, Straif K; International Agency for Research on Cancer Handbook Working Group. The IARC Perspective on Colorectal Cancer Screening. N Engl J Med. 2018;378:1734-40.
29. Favoriti P, Carbone G, Greco M, Pirozzi F, Pirozzi RE, Corcione F. Worldwide burden of colorectal cancer: a review. Updates Surg. 2016;68:7-11.

ORIGINAL ARTICLE

AG-2019-178
doi.org/10.1590/S0004-2803.202000000-33

Portuguese version of the SNAQ questionnaire: translation and cultural adaptation

Mariana Staut **ZUKERAN**[1], Ivan **APRAHAMIAN**[2], Beatriz Martins **VICENTE**[1] and Sandra Maria Lima **RIBEIRO**[1,3]

Received: 29 December 2019
Accepted: 20 February 2020

ABSTRACT – **Background** – Poor appetite is common through the aging process and increases the risk of weight loss, protein-energy malnutrition, immunossupression, sarcopenia and frailty. The Simplified Nutritional Appetite Questionnaire (SNAQ) has the aim to monitor appetite and identify older adults at risk of weight loss. **Objective** – To describe the process of translation and cultural adaptation to Brazilian Portuguese of the SNAQ. **Methods** – The translation and cultural adaptation was developed in five steps: translation (by three of the authors of the manuscript and assembled by consensus), backtranslation (by an English native speaker), semantic evaluation (by one verontologist and one nutritionist), comprehension of content (by nutrition specialists and by a group of older persons), pre-test and the SNAQ final version development. **Results** – The SNAQ Portuguese version maintained the original version meaning and referral. To achieve this feature, the process required some modifications to improve the understanding of older persons, such as inclusion of other options to the answers of some questions, rewritten of one question and inclusion of a meal definition. **Conclusion** – SNAQ questionnaire has been successfully translated and adapted to Portuguese. As our next step, we are validating this tool in different clinical settings in Brazil.

HEADINGS – Validation study. Surveys and questionnaires. Weight loss. Appetite. Aging.

INTRODUCTION

The aging process is commonly accompanied by poor appetite and/or decreased food intake. This condition, named anorexia of aging (AA), may result from psychological, sociological and physiological factors. AA is mostly associated with unfavorable prognosis[1-3]. Loss of appetite and reduction of food intake lead to weight loss, increased risk of protein-energy malnutrition, immunosuppression, sarcopenia and frailty[2]. The prevalence of AA is reported to be around 25% in community-dwelling older adults and 62% in hospital inpatients. Nursing home settings present the highest prevalence of 85%[2,4].

Most of undernutrition screening tools evaluate loss of appetite as a component of multiple nutritional domains instead of an individual construct. The importance of evaluating specifically loss of appetite is to enable interventions, such as meal adjustments and/or supplementation, before the onset of weight loss and/or risk of malnutrition. The Simplified Nutritional Appetite Questionnaire (SNAQ) was developed as a smaller version of the Council of Nutrition Appetite Questionnaire (CNAQ), with the aim to monitor appetite and identify persons at risk for weight loss. The SNAQ is a 4-question screening tool validated in community-dwelling and institutionalized older adults, as well as among younger adults. The questions comprehend information on self-perception of appetite, satiety after meals, food taste and number of meals consumed daily. A score lower than 14 points identify persons at risk of losing significant weight (≥5% of body weight) in the next six months[2].

Considering the lack of standardized, translated and culturally adapted tools to assess appetite in Brazil[2,4,5], the aim of this study was to perform the translation and cultural adaptation of the SNAQ to Brazilian Portuguese.

METHODS

The procedures adopted in the present work were based on the "Guidelines for the process of cross-cultural adaptation of self-report measures"[6], together with other published translations of questionnaires to Brazilian Portuguese[7-9]. To achieve our aims, we divided the processes in five steps, as described below and outlined at FIGURE 1.

Step 1. Translation and back translation procedures

The original English version (OV) of the SNAQ was simultaneously translated by three authors of this manuscript, being two dietitians [PT1 (SMLR) and PT2 (MSZ)] and one geriatrician (PT3, IA), all of them are Brazilian Portuguese native speakers. A common translation (CT) was obtained after a consensus meeting between the three professionals. The CT was afterwards back translated (BT) by an English native speaker.

Step 2. Semantic evaluation

The CT and BT were submitted to a semantic evaluation by one gerontologist and one dietitian; those professionals did not take part on the first step of the project. They made suggestions related to some words or terms they considered more familiar to older adults. From these suggestions, we constructed the SNAQ Portuguese Preliminary version (PPV), which was simultaneously submitted to the Steps 3 and 4.

Declared conflict of interest of all authors: none
Disclosure of funding: no funding received
[1] Universidade de São Paulo, Faculdade de Saúde Pública, São Paulo, SP, Brasil. [2] Faculdade de Medicina de Jundiaí, Jundiaí, SP, Brasil. [3] Universidade de São Paulo, Escola de Artes Ciências e Humanidades, São Paulo, SP, Brasil.
Corresponding author: Mariana Zukeran. E-mail: marizukeran@hotmail.com

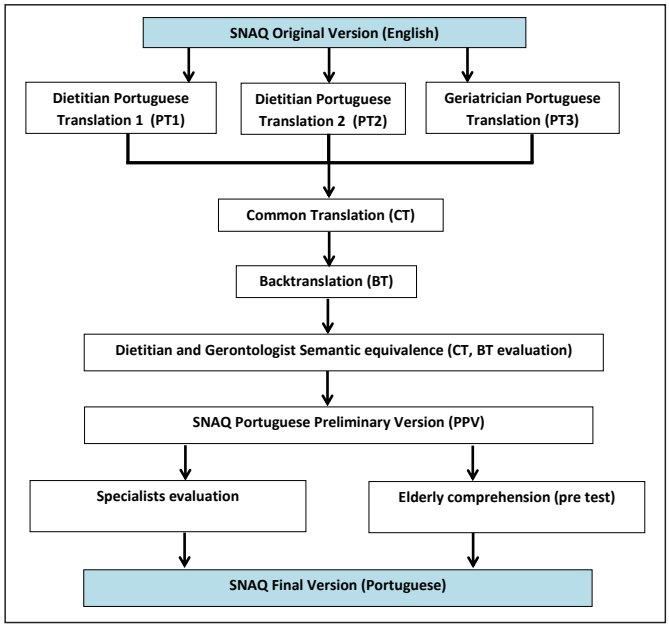


FIGURE 1. SNAQ translation and cultural adaptation flowchart.

Step 3. Comprehension of content

The OV and the PPV were sent to 25 Brazilian dietitians who were specialists working with older adults in different settings (primary care, specialized ambulatory clinics, hospitals and nursing homes). The contact and submission of the material for analysis were made using the e-mail messages and Google Forms resources. The dietitians were instructed to carefully read both versions and answer numeric scales for each of the SNAQ questions, as following: (-1) non-equivalent, (0) undecided and (+1) equivalent. If considered necessary, the professionals could suggest changes on the PPV. The comprehension level was evaluated through a scale of 0 to 5 (0 for "not understand at all" and 5 for "perfectly understand with no doubts") for each question. Sixteen dietitians returned the questionnaire to the authors.

Step 4. Pre-test of PPV

The pre-test of SNAQ was performed with a group of older adults who attend to an Open University in São Paulo, Brazil. This older adults signed a term of agreement before participation. The researchers evaluated the older adults' comprehension according to the answers and doubts demonstrated as they answered the SNAQ. Older adults' comprehension of each question was punctuated in the same way as in the Step 3 (a score from 0 to 5, where 0 means "not understand at all" and 5 means "perfectly understand with no doubts").

Step 5. Validity of content and SNAQ final version

The validity of content was calculated according to the percentage of equivalent answers for each question. The mean and SD values for the oral comprehension (both specialists and older adults) were calculated with SPSS software version 23.

After the analysis of the comprehension and the content validity, the researches included observations and changed some terms to improve the SNAQ comprehension and to obtain the final version of the tool. The decision about the best terms to be used in the final version was made in a consensus meeting between two of the researchers (MSZ and SMLR). Most of the choices were based on the majority of the responders (both specialists and older adults). However, specific decisions were made with the help of electronic communications with one of the authors of the OV of the SNAQ (JEM).

Ethical standards

This study was derived from a broader research study and all procedures were conducted in accordance with the resolution 466/12 from CNS and approved by the Faculty of Medicine of Jundiaí Ethics Committee under the CAAE number: 12535218.5.3001.5412.

RESULTS

FIGURE 2 depicts the specialists' suggestions and the final decisions about each question, and TABLE 1 shows the level of comprehension of the Brazilian Portuguese version of SNAQ. The content validity was above 80% for all the questions. The higher percentage was for question 1 (93.8%) and the lowest for question 3 (81.3%). The oral comprehension mean values were very similar for both specialists and older adults. Question 1 had the best oral comprehension value.

Original version	Preliminary version	Specialists suggestions	Final version
Very poor / poor	Muito ruim / ruim	Sem appetite (suggested by 2 specialists)	Muito ruim / ruim
Average	Mediano	Regular (suggested by 1 specialist)	Mediano
Meal	Refeição	Prato (suggested by 1 specialist)	Refeição
Feel full	Cheio	Satisfeito (suggested by 1 specialist)	Satisfeito

FIGURE 2. Translation and suggestions on the translation and cultural adaptation of the SNAQ questionnaire.

TABLE 1. Descriptive analysis of both specialists' and older adults' comprehension of the PPV of the SNAQ questionnaire.

Questions	Specialists (n=16)		Older adults (n=20)
	Content validity	Oral comprehension	Oral comprehension
	(%)	Mean (SD)	Mean (SD)
1	93.8	4.9 (0.3)	5.0 (0.2)
2	87.5	4.6 (0.8)	4.7 (0.7)
3	81.3	4.8 (0.5)	4.2 (0.8)
4	87.5	4.8 (0.6)	4.7 (0.6)

PPV: Portuguese preliminary version.

The terms "very poor", "poor" and "average" (answers of the questions 1 and 2) were translated to "muito ruim", "ruim" and "mediano". Although two specialists suggested modifications to "sem apetite" and "regular", the PPV terms were maintained, based on the majority's acceptance of the PPV. However, not all the decisions were made based on the majority. Specifically, the term "feel full" was initially translated to "cheio", but it was changed to "satisfeito" at the final version, because it implies the concept of "eat enough food", according to the electronic communication with the author of the OV. In addition, the researchers also proposed to maintain the term "refeição" instead of "prato" (a specialist's suggestion) on the last question of the SNAQ. However, to avoid misunderstandings, we decided to include a small note regarding the meaning of the word "meal", as following: "Consider participant definition of meal (breakfast, lunch and dinner) being the largest eating occasion in each period: morning, afternoon and night[10].

The SNAQ test was conducted with 20 older adults, mean age 69.1 (DP 6.8), from which 75% were female. During the SNAQ pre-test the researches noticed the older adults presented difficulties in answering about food taste (question 2), especially when they use to prepare their own meal (because they always cook what and how they like). As such, on the answer "e" (food tastes very good) it was added the option "I prepare food as I like".

Question 3 had the lowest mean value on older adults' comprehension because they had difficulty to choose between the long answers; in addition, they had doubts to answer in the situations in which they "usually eat everything". The necessary changes in this case were to increase the question and reduce the answers, as following: "when I eat, I feel full after eating": (a) only a few mouthfuls; (b) about a third of a meal; (c) over half of a meal; (d) most of the meal; (e) I hardly ever feel full; I eat everything".

FIGURE 3 summarizes the description of the OV, PPV and Portuguese final version of SNAQ.

DISCUSSION

In the present study, we performed the SNAQ translation, back translation and adaptation to Brazilian Portuguese. Several studies have emphasized the necessity to translate and culturally adapt different tools in order to guarantee that the data obtained express the originally intended information[6-8]. The adaptation process requires that the translation method assures the original meaning and, simultaneously, enables comprehension according to the other culture[6]. We described here the procedures used on the SNAQ translation and adaptation do Portuguese which included three translations, back translation, semantic equivalence, content validity and comprehension by specialists and pre-test with older adults. In addition, we solved some issues with one of the authors of the questionnaire OV.

Original version	Preliminary version	Final version
My appetite is	**Meu apetite é**	**Meu apetite é**
a. Very poor	a. Muito ruim	a. Muito ruim
b. Poor	b. Ruim	b. Ruim
c. Average	c. Mediano	c. Mediano
d. Good	d. Bom	d. Bom
e. Very good	e. Muito bom	e. Muito bom
Food tastes	**A comida tem sabor**	**A comida tem sabor**
a. Very bad	a. Muito ruim	a. Muito ruim
b. Bad	b. Ruim	b. Ruim
c. Average	c. Mediano	c. Mediano
d. Good	d. Bom	d. Bom
e. Very good	e. Muito bom	e. Muito bom / eu preparo a comida como gosto
When I eat	**Quando eu como**	**Quando eu como, eu me sinto satisfeito após comer**
a. I feel full after eating only a few mouthfuls	a. Eu me sinto cheio após comer somente algumas colheradas/garfadas	a. Somente algumas colheradas/garfadas
b. I feel full after eating about a third of a meal	b. Eu me sinto cheio após comer menos da metade ou cerca de 1/3 da refeição	b. Menos da metade ou cerca de 1/3 da refeição
c. I feel full after eating over half of a meal	c. Eu me sinto cheio após comer metade da refeição	c. Mais da metade da refeição
d. I feel full after eating most of the meal	d. Eu me sinto cheio após comer a maior parte da refeição	d. A maior parte da refeição
e. I hardly ever feel full	e. Eu raramente me sinto cheio	e. Eu como tudo / Eu raramente me sinto satisfeito
Normally I eat	**Normalmente eu como**	**Normalmente eu como**
a. Less than one meal a day	a. Menos do que uma refeição por dia	a. Menos do que 1 refeição por dia
b. One meal a day	b. Uma refeição por dia	b. Uma refeição por dia
c. Two meals a day	c. Duas refeições por dia	c. Duas refeições por dia
d. Three meals a day	d. Três refeições por dia	d. Três refeições por dia
e. More than three meals a day	e. Mais do que três refeições por dia	e. Mais do que três refeições por dia
		**Considerar a visão do participante sobre refeição (café da manhã, almoço e jantar) sendo o consumo da maior quantidade de alimentos em cada período: manhã, tarde e noite.*

FIGURE 3. SNAQ original, preliminary and final Portuguese versions.

Considering the possibility of using the questionnaire in different health care settings, the specialists from those workplaces were invited for the content and comprehension analysis. SNAQ was originally validated to community-dwelling and institutionalized older adults, as well as to young adults. In our study, we had to make some changes, such as adding other answer options to some questions, rewriting question 3, and including a meal definition to improve understanding.

Because of its easy clinical use, the SNAQ questionnaire has also been translated and validated in different countries such as Japan, Australia and Malaysia[11-14]. In Brazil, it was previously translated and culturally adapted to a very specific population (older adults with cardiac diseases) from a specific setting in the South area of the country[15]; we understand that our present study added important informations to the previous one, since we adapted the tool to community-dwelling older adults and obtained the opinion of professionals from different health care setting.

CONCLUSION

The SNAQ questionnaire has been successfully translated and adapted to Portuguese. As continuation of our findings, we are currently validating the tool, investigating the sensibility and specificity in identifying the risk of weight loss in older adults from different settings and in adults with chronic conditions.

ACKNOWLEDGEMENTS

The authors thank to Henrique Salmazo and Lilian Barbosa Ramos for the initial suggestions, and to all the dietitians who agreed to give their opinion on the comprehension of the SNAQ Portuguese version. We are also grateful to João Valentini Neto for the help in collecting the data.

Authors' contribution

Zukeran MS: conceptualization, data curation, formal analysis, methodology, project administration, writing-original draft. Aprahamian I: writing-review and editing. Vicente BM: data curation, methodology. Ribeiro SML: conceptualization, data curation, formal analysis, methodology, project administration, supervision, writing-review and editing.

Orcid

Mariana Staut Zukeran: 0000-0002-7986-7664.
Ivan Aprahamian: 0000-0003-3806-7895.
Beatriz Martins Vicente: 0000-0002-5959-120X.
Sandra Maria Lima Ribeiro: 0000-0003-3150-516X.

Zukeran MS, Aprahamian I, Vicente BM, Ribeiro SML. Versão em português do questionário SNAQ: tradução e adaptação cultural. Arq Gastroenterol. 2020;57(2):178-181.

RESUMO – **Contexto** – A perda de apetite é comum durante o envelhecimento e aumenta o risco de perda de peso, desnutrição energético-proteica, imunossupressão, sarcopenia e fragilidade. O *Simplified Nutritional Appetie Questionnaire* (SNAQ) tem como objetivo monitorar o apetite e identificar idosos sob risco de perda de peso. **Objetivo** – Descrever o processo de tradução e adaptação cultural para o português do Brasil o questionário SNAQ. **Métodos** – A tradução e adaptação cultural foram realizadas em etapas: tradução (por três autores do manuscrito e grupo para consenso), retrotradução para versão original (por inglês nativo), avaliação semântica (gerontólogo e nutricionista), compreensão de conteúdo (por nutricionistas especialistas e por um grupo de idosos), pré teste e desenvolvimento da versão final. **Resultados** – A versão em português do SNAQ manteve o significado da versão original. Para alcançar este resultado foram necessárias algumas modificações durante o processo para aperfeiçoar a compreensão dos idosos, como a inclusão de outras opções para respostas de algumas questões, revisão de escrita de uma das questões e inclusão de uma definição para o que é refeição. **Conclusão** – A tradução e adaptação cultural do questionário SNAQ foram bem sucedidas. A próxima etapa será a validação desta ferramenta em diferentes contextos clínicos no Brasil.

DESCRITORES – Estudo de validação. Inquéritos e questionários. Perda de peso. Apetite. Envelhecimento.

REFERENCES

1. Morley JE, Silver AJ. Anorexia in the elderly. Neurobiol Aging. 1988;9:9-16.
2. Wilson MM, Thomas DR, Rubenstein LZ, Chibnall JT, Anderson S, Baxi A, et al. Appetite assessment: simple appetite questionnaire predicts weight loss in community-dwelling adults and nursing home residents. Am J Clin Nutr. 2005;82:1074-81.
3. Wysokinski A, Sobow T, Kloszewska I, Kostka T. Mechanisms of the anorexia of aging-a review. Age (Dordr). 2015;37:9821.
4. Cox NJ, Ibrahim K, Sayer AA, Robinson SM, Roberts HC. Assessment and Treatment of the Anorexia of Aging: A Systematic Review. Nutrients. 2019;11:144.
5. Roberts HC, Lim SER, Cox NJ, Ibrahim K. The Challenge of Managing Undernutrition in Older People with Frailty. Nutrients. 2019;11:808.
6. Beaton DE, Bombardier C, Guillemin F, Ferraz MB. Guidelines for the process of cross-cultural adaptation of self-report measures. Spine (Phila Pa 1976). 2000;25(24):3186-91.
7. Roedinger MA, Marucci MFN, Latorre MRDO, Hearst N, Oliveira C, Duarte YAO, et al. Cross-cultural adaptation to the Portuguese language of the Determine Your Nutritional Health® screening method for the elderly in assisted living accommodation. Ciênc Saúde Coletiva. 2017;22:509-18.
8. Conti MA, Scagliusi F, Queiroz GK, Hearst N, Cordas TA. Cross-cultural adaptation: translation and Portuguese language content validation of the Tripartite Influence Scale for body dissatisfaction. Cad Saude Publica. 2010;26:503-13.
9. Silveira MB, Saldanha RP, Leite JCC, Silva TOFD, Silva T, Filippin LI. Construction and validation of content of one instrument to assess falls in the elderly. Einstein (Sao Paulo). 2018;16(2):eAO4154.
10. St-Onge MP, Ard J, Baskin ML, Chiuve SE, Johnson HM, Kris-Etherton P, et al. Meal Timing and Frequency: Implications for Cardiovascular Disease Prevention: A Scientific Statement From the American Heart Association. Circulation. 2017;135:e96-e121.
11. Tokudome Y, Okumura K, Kumagai Y, Hirano H, Kim H, Morishita S, et al. Development of the Japanese version of the Council on Nutrition Appetite Questionnaire and its simplified versions, and evaluation of their reliability, validity, and reproducibility. J Epidemiol. 2017;27:524-30.
12. Nakatsu N, Sawa R, Misu S, Ueda Y, Ono R, Yaxley A, et al. Reliability and validity of the Japanese version of the simplified nutritional appetite questionnaire in community-dwelling older adults. Geriatr Gerontol Int. 2015;15:1264-9.
13. Yaxley A, Crotty, M, Miller, M. Identifying Malnutrition in an Elderly Ambulatory Rehabilitation Population: Agreement between Mini Nutritional Assessment and Validated Screening Tools. Healthcare. 2015;3:822-9.
14. Hanisah R, Suzana S, Lee FS. Validation of screening tools to assess appetite among geriatric patients. J Nutr Health Aging. 2012;16:660-5.
15. Sties SW, Gonzáles AIs, Viana MdS, Brandt R, Bertin RL, Goldfeder R, et al. Questionário nutricional simplificado de apetite (QNSA) para uso em programas de Reabilitação cardiopulmonar e metabólica. Rev Bras Med Esporte. 2012; 18:313-7.

ORIGINAL ARTICLE

AG-2020-05
doi.org/10.1590/S0004-2803.202000000-34

Hospital morbidity and colorectal cancer mortality: implications for public health in Brazil

Ramona Garcia Souza **DOMINGUEZ**[1] and Ana Luiza **BIERRENBACH**[2]

Received: 20 January 2020
Accepted: 25 March 2020

ABSTRACT – **Background** – Colorectal cancer is a serious public health problem and one of the most common cancer worldwide. Countries around the world have shown different trends. While incidence and mortality rates for colorectal cancer are on an upward trend in developing countries, these rates have been on a downward trend in most developed countries. **Objective** – To analyze the temporal trend of morbimortality by colorectal cancer in Brazil between 2002 and 2016. **Methods** – Descriptive, time series research. Data were extracted from the national information systems for hospitalizations and deaths of the respective years. **Results** – There were increasing trends in hospital morbidity and mortality from colorectal cancer in all regions of the country, with the very elderly individuals dying at a higher rate. Women (52.1%) were more affected than men, but death rates were higher for males aged 60 years or more. Regional disparities were evident, with almost 80% of deaths occurring in the South and Southeast, with the largest annual increase in the South and the lowest in the North. Regarding hospitalization, South and Southeast presented higher annual growths. **Conclusion** –These data add knowledge about the profile of public hospitalizations and deaths, reaffirming that colorectal cancer contributes to an important burden of disease and mortality in Brazil. These elements have implications for the review of colorectal cancer prevention and control strategies, as well as for public health investments.

HEADINGS – Colorectal neoplasms, mortality. Morbidity. Public health. Medical oncology.

INTRODUCTION

Cancer is a serious worldwide public health problem. The Brazilian National Cancer Institute (INCA) estimated for the biennium 2018–2019, in Brazil, 17,380 new cases of colorectal cancer (CRC) in men and 18,980 in women. As a result, CRC appears as the third type of cancer with greatest incidence in the Brazilian population, occupying 2nd place among women and 3rd place among men[1].

Countries around the world have different CRC mortality trends. The Globocan report demonstrates that the incidence and mortality rates for CRC are on an upward trend in developing countries, such as Colombia and Costa Rica, while in the developed countries these rates have remained on a downward trend for many years (USA, New Zealand, Australia and Canada). Such disparities may be associated to different lifestyle habits, as well as to the inequity of the availability of resources for early diagnosis and treatment[2].

A study in 34 European countries and in the United States (USA), with data from the World Health Organization (WHO) in the period of 1970–2011, demonstrated a downward trend with a reduction in mortality of over 25% among men and 30% among women in Austria, Belgium, Germany, Czech Republic, Luxembourg and Ireland, for example. In the United Kingdom, there was a 30% drop in mortality rates for both genders (1989–2011), with an annual decrease of 2.0% and in the USA the reduction reached 39.8% for men and 38.8% for women[3].

Due to its high morbidity and mortality, CRC brings relevant social and economic consequences to the societies. In the USA, for example, deaths by CRC of individuals between the ages of 50 and 74, occurring between 2008 and 2012, resulted in approximately US$ 2 billion dollars in loss of productivity per year, being considered as potentially avoidable deaths[4].

CRC, in general, affects individuals of ages 55-60 or over, in whom, approximately 80% of the cases, the disease arises in a sporadic manner. Apart from age, other risk factors are well characterized, such as individual and family clinical history, occurrence of intestinal polyps, diet, obesity, alcoholism, smoking and diabetes, with some of these being changeable and/or preventable[5].

Access to diagnosis services and treatment, as well as to strategies for screening the disease can be considered as factors that have the potential of decreasing the incidence and, at the same time, directly reducing the CRC mortality rates[6].

To broaden the discussion on health services and in order to be able to report data on hospital incidence, this research aggregates the data analysis on hospital morbidity and mortality for CRC, inexistent in the above-mentioned studies and a scant subject of literature in Brazil. This information enables assessment and guidance on the adoption of control and prevention strategies in the scope of public policies, considering regional differences and socioeconomic implications. Accordingly, the objective of this study was to analyze the temporal trend of morbidity and mortality due to CRC in Brazil, between 2002 and 2016.

Declared conflict of interest of all authors: none
Disclosure of funding: no funding received
[1] Universidade Federal do Recôncavo da Bahia (UFRB), Santo Antônio de Jesus, BA, Brasil. [2] Instituto de Ensino e Pesquisa do Hospital Sírio Libanês (IEP-HSL), São Paulo, SP, Brasil.
Corresponding author: Ramona Garcia Souza Dominguez. E-mail: ramonagarcia@ufrb.edu.br.

METHODS

The study used data on deaths and hospitalizations due to CRC in Brazil, in the period between 2002 and 2016. Individual data were extracted from the Information System on Mortality (*Sistema de Informações sobre Mortalidade* – SIM) and aggregated data from the Hospital Information System (*Sistema de Informações Hospitalares* – SIH). Both systems are public and data can be downloaded from the Internet.

Only the underlying causes of death registered in accordance with the tenth review of the International Classification of Diseases (ICD-10), with codes C18.0–C18.9 for colon and C19 to C21 for rectal cancer, rectosigmoid junction, anal channel and anus, were considered as deaths by CRC. For hospitalizations, these same codes were used to classify the field designate as the main diagnosis. Population data were originally obtained from the Brazilian Institute of Geography and Statistics (IBGE).

The crude and standardized annual rates of notification of death and hospitalization due to CRC per 100,000 persons per year were calculated for each region of the country, gender and age group. The annual increase in the rates was estimated using simple linear regression models. $P<0.05$ values were considered as statistically significant. For data management and analysis, Excel program and Stata software version 12 were used. The Ethics Committee of the Syrian Lebanese Hospital approved the study under CAAE no. 29183314.1.0000.5461.

RESULTS

In this research, a rising trend in hospital morbidity and mortality rates due to CRC was observed in Brazil between 2002 and 2016 (FIGURE 1). Hospitalization rates for CRC presented an annual increase of 1.48 per 100,000 persons per year ($P<0.001$) and a standardized rate of 0.96 per 100,000 ($P<0.001$). The CRC mortality rate presented an annual increase of 0.26 deaths per 100,000 person-years ($P<0.001$) and a standardized rate of 0.06 per 100,000 person-years ($P<0.001$).

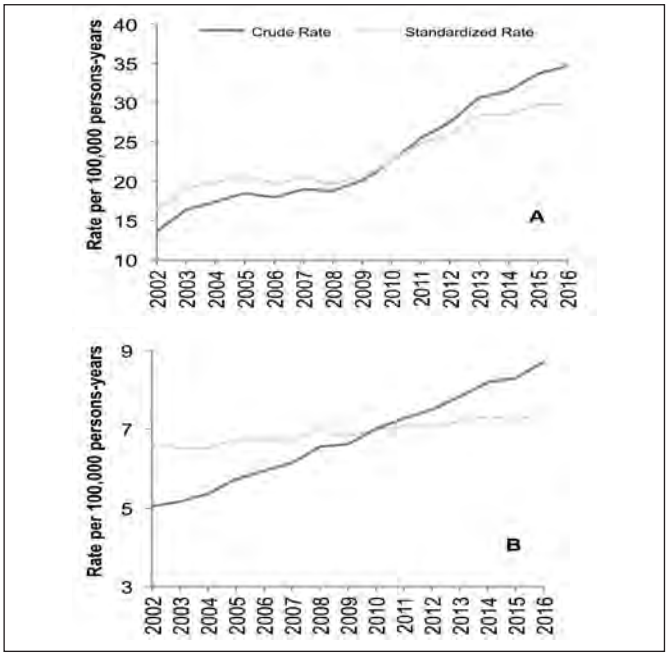


FIGURE 1. Colorectal cancer morbidity and mortality rates. Brazil from 2002 to 2016. (A) Hospitalization; (B) Deaths.

The comparison between the years 2002 and 2016 demonstrated an increase in the hospitalization and death rates by CRC, considering the total amount of cases and separately for both genders, for each age group and region. The highest hospitalization rate was found in individuals of ages 70–79 years (175.4 per 100,000) and the highest death rate occurred in the elderly age group (≥80 years, 107.1 per 100,000).

The total number of women deceased with CRC as the underlying cause of death was higher than that of the men, but the proportion and death rates increased with increasing age for both genders (TABLE 1).

TABLE 1. Colorectal cancer morbidity and mortality by epidemiologic aspects. Brazil from 2002 to 2016.

Year	2002						2016					
	Hospitalization			Death			Hospitalization			Death		
Variable	N	%	Rate*	N	%	Rate*	N	%	Rate*	N	%	Rate*
Sex												
Male	12,307	51.9	14.4	4,087	46.6	4.8	35,531	50.4	35.8	8,829	49.9	8.9
Female	11,425	48.1	12.9	4,683	53.4	5.3	34,944	49.6	33.6	8,868	50.1	8.5
Age												
0–49	11,903	50.2	8.2	1,241	14.1	0.9	15,604	22.1	9.9	1,783	12.3	1.2
50–59	3,647	15.4	26.6	1,411	16.1	10.3	17,381	24.7	79.1	2,939	17.3	13.4
60–69	3,955	16.7	44.9	2,078	23.7	23.6	20,349	28.9	153.6	4,476	23.8	33.8
70–79	3,180	13.4	65.2	2,444	27.9	50.1	12,935	18.4	175.4	4,388	24.9	59.5
80+	1,047	4.4	51.0	1,596	18.2	77.7	4,206	6.0	116.9	3,853	21.7	107.1
Regions												
Midwest	1,398	5.9	11.6	441	5.0	3.6	4,560	6.5	29.4	1,109	6.3	7.1
Northeast	3,693	15.6	7.6	878	10.0	1.8	10,370	14.7	18.4	2,690	15.2	4.8
North	733	3.1	5.4	164	1.9	1.2	1,723	2.4	9.8	634	3.6	3.6
Southeast	11,132	46.9	15.0	5,295	60.4	7.2	33,329	47.3	39.1	9,719	54.9	11.4
South	6,776	28.6	26.3	1,992	22.7	7.8	20,493	29.1	71.3	3,546	20.0	12.3
Total	23,732	–	13.6	8,772	–	5.0	70,475	–	34.7	17,698	–	8.7

* Rate by 100,000 person-years.

Regional disparities were evident. The South and Southeast regions concentrate almost 80% of hospitalizations and the highest death rates due to CRC. Hospitalization rates were lower in the North and Northeast regions. In this study, it was observed that death rates increased mainly in Northeast and Midwest regions of Brazil.

The trend analysis of the hospital morbidity and mortality rates by age groups and gender evidenced a similar pattern between men and women aged 60 and younger. However, rates were predominant for the male gender in the other age groups. In 2007, specifically among people aged 80 years and older, there was an inversion in the mortality rate with predominance of deaths among men, which was maintained until the end of the studied period (FIGURE 2).

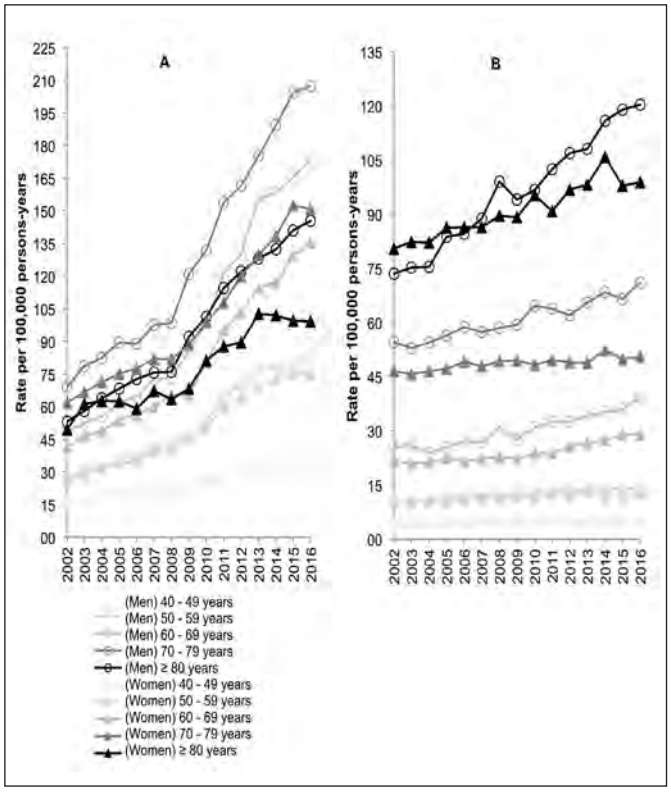


FIGURE 2. Colorectal cancer morbidity and mortality rates by age groups and sex. Brazil from 2002 to 2016. (A) Hospitalization; (B) Deaths.

Comparing data by regions, their hospitalization rates showed significant growing trends due to CRC (P<0.001), with exception to the Northern region. This growth was more significant in the South (3.3 per 100,000/year), representing an increase of over 170% in the comparison between 2002 and 2016, followed by the Southeast (+1.8/100,000) and Midwest (+1.1/100,000/year). In the Northeast, the annual increase was of 0.67 hospitalizations per 100,000/year (P<0.001) (FIGURE 3).

There was also a steady increase in the death rates for CRC for all regions in Brazil. The growing trends were statistically significant and greater in the South (0.33 deaths per 100,000/year) and Southeast (0.31 per 100,000/year), overcoming the growth curve for Brazil as a whole. The third highest mortality rate for CRC was observed in Midwest with an annual increase of 0.27 deaths per 100,000/year, followed by Northeast (0.22 deaths per 100,000/year) and Northern region (0.15 deaths per 100,000/year) (FIGURE 3).

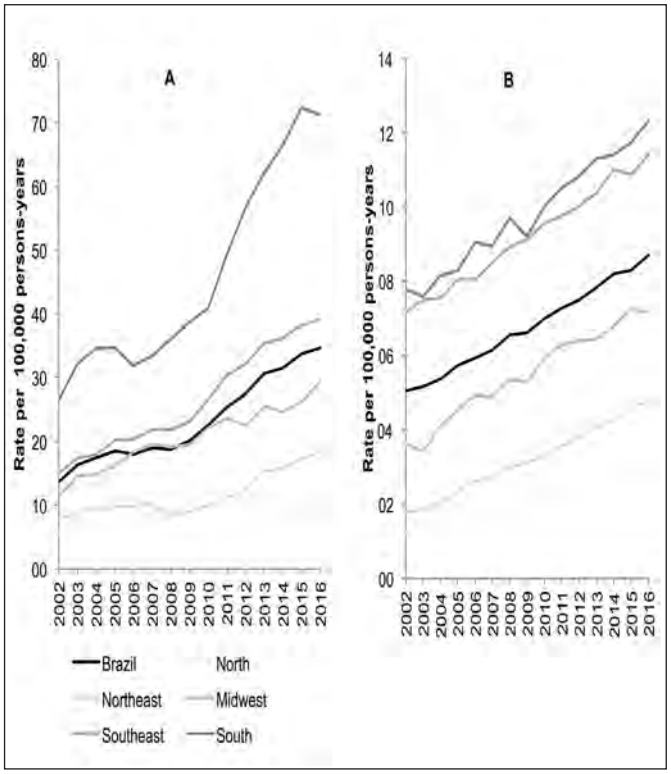


FIGURE 3. Colorectal cancer morbidity and mortality rates by regions. Brazil from 2002 to 2016. (A) Hospitalization; (B) Deaths.

DISCUSSION

In this study, a growing trend was observed in the morbidity and mortality rates for CRC in Brazil. It was possible to verify that CRC hospitalizes and kills more elderly patients and, despite the number of women deceased being superior to men, rates were higher for the male gender, especially in the age group of 60 years and older.

Multiple factors are involved to explain this increasing trend. Part of this increase reflects epidemiological changes, with the consequent increase in the CRC incidence, due to greater exposure to risk factors, as well as to access to treatment difficulties that contribute towards reducing the survival rate of the patients.

However, the increase in the capacity of the health system to perform the diagnosis of the disease due to better access to health, training and technology over the study period can also be considered as a factor that could be contributing to an increase in these rates. Despite greater overall access to diagnosis, it is possible that this is occurring late in the natural history of the CRC disease, impairing treatment and aggravating the prognosis of patients[7].

Similarly, the growing trends in morbidity and mortality due to CRC should also be analyzed under the viewpoint of the changes, usually for the better, that occurred in the respective information systems throughout the studied period, as mentioned below.

Among the factors influencing high-incidence and mortality are the increasing life expectancy in the country[1], increased exposure to risk factors and decreased exposure to known protective factors for the disease. The demographic and epidemiological transition in Brazil should also be highlighted, with the aging of the population and increased deaths due to chronic diseases[7].

Age is an important risk factor for diseases that have a slow evolution and where the exposure to carcinogens accumulates over time, as is CRC. Almost 80% of CRC cases can be classified as sporadic, in other words, products of an insidious evolution and consequently more frequent in the elderly[5].

Despite this, the increasing life expectancy throughout the period studied explains only part of the raising rates. This is evidenced in the comparison of the standardized and crude rates, for both hospitalization and death. The crude rates were, as expected, more inclined than the standardized rates, which reflects that the aging population is not the only factor explaining the increasing trend.

Other risk factors commonly involved include individual and family clinical history for the disease, diets with a high content of fat and red meat, obesity, alcoholism, smoking, diabetes and inflammatory diseases of the colon[8].

Differently from what was observed in Brazil, the CRC incidence declined in the USA which is attributed to a lower exposure to known risk factors of the disease (consumption of processed meat) and greater exposure to protection factors (use of anti-inflammatory non-hormone analgesics, hormone reposition therapy and statins), as well as the availability of diagnostic resources and early removal of intestinal polyps with or without the presence of *in situ* tumors[6].

In England, it was evidenced that living in economically underprivileged areas impairs access to health and the care of patients with CRC[9]. Socioeconomic and cultural discrepancies among the regions influence not only the exposure to risk factors, which tends to cause a greater incidence of CRC among the residents of more developed regions, but also influence access of the patients to hospital services in Brazil, being unfavorable for residents of the poorer regions[10,11].

The improvement of access to diagnosis in Brazil observed over the study period may also have affected CRC mortality for the simple fact that deaths previously incorrectly recorded as unspecific underlying causes (for example, cancer code without any specific location) or ill-defined, were correct registered as CRC in underlying cause of death.

In Brazil, there was an important decline in the number of ill-defined causes of death, resulting from a well-succeeded intervention of the Ministry of Health. This proportion is considered as an important quality indicator of mortality information systems[12].

Another indicator is the coverage of the information system. In Brazil, the death register coverage climbed from 80% in 1980–1991 to over 95% in 2000-2010[13]. There are still losses in the municipalities that are further away from the capital cities, mainly in the elderly group. Nevertheless, the proportion of deaths with ill-defined causes decreased during the period of the study, especially in the North and Northeast regions.

The investigations of ill-defined causes of death demonstrated that, after reclassification, cancers had a lower representation, contrary to the endocrine diseases, mental disorders, nervous system, circulatory system and maternal causes[14]. These findings reveal that the representativeness of CRC among the ill-defined causes is substantially lower in relation to other diseases. In other words, improvements in the SIM cannot be separately responsible for the increase in CRC mortality, including North and Northeast regions.

As regards the SIH, despite the fact that its use has been increasingly common in epidemiological studies, the quality of information can be questioned in relation to the selection of the codes used to describe the main and the subsidiary clinical conditions[15]. In 2008, changes were made in the table of values used by SUS (public health system) to pay for hospital services, which could interfere with trends in specific codes, but there was no marked change at that time in trends observed for CRC.

As a result of the oncological healthcare network expansion, which started as a public policy in 2005[16], the capacity and access to CRC diagnosis presented an improvement in the period studied. In 2016, there were 510 qualified services for oncology in Brazil but, when regional distribution is analyzed, considering only qualified public hospitals for this field of expertise, it is evident that most of these services (72%) are located in economically developed regions (South and Southeast)[17].

However, even in the locations where this network is physically implemented, there are still difficulties in access resulting from incipient regulatory system and lack of professionals (especially for surgeons and oncologists), as well as shortage of investments in treatment, primary and secondary preventions[18].

Early detection of CRC can lead to improvements in survival. Nevertheless, the structure of the oncological healthcare network does not yet enable a timely and equitable access to cancer diagnosis and treatment, despite the increase in the number of qualified establishments for this medical specialty. The reality of the Brazilian public health has been marked by insufficient and/or misguided investments, low incorporation of new technologies and limited access to effective treatment[18]. All of these factors contribute to advanced-stage cancer at the time of diagnosis.

Data related to new cases of CRC in the municipality of São Paulo, demonstrates that diagnosis occurs in advanced stages: 28.2% in stage III and 23.2% in stage IV of the TNM staging system, which assesses the size and extent of the main tumor (T), number of nearby lymph nodes that have cancer (N) and presence of metastases (M); consequently, a very poor prognosis[5].

The late detection of CRC negatively influences patient's survival, collaborating to an increase in the morbidity and mortality rates observed in this study. The fact that the rates have a rising trend necessarily generates questions on the prioritization of primary and secondary prevention services, emphasizing the importance of the correct management of the resources allocated to the oncological healthcare network.

Early detection of CRC presents the peculiarity of enabling the prevention of the disease, permitting the identification and removal of intestinal polyps that have a indolent development (leading to a reduction of occurrence), diagnosis in early stages which, when adequately treated, can raise the survival rate in five years to 90% and reduce mortality[19].

Population-based screening for cancer encompasses a complex structure that must meet certain criteria in order to guide the policies in the countries that consider the organization of these programs: 1) an important public health problem; 2) accepted treatment for patients with recognized disease; 3) availability of facilities for diagnosis and treatment; 4) recognizable latent or early symptomatic stage; 5) suitable test or examination; 6) test should be acceptable to the population; 7) natural history of the disease must be adequately understood; 8) agreed policy on whom to treat as patients; 9) cost-effectiveness of the case-finding must be economically balanced in relation to possible expenses on medical care as a whole; 10) case-finding should be a continuing process[20].

Population-based screening for CRC meets those criteria. The experience in CRC screening program, developed in USA, demon-

strated a reduction in CRC incidence and mortality rates in men and women since the 1980s[20]. The extension of CRC screening programs is a pertinent and cost-effective strategy, considering that the costs of its implementation, despite being high, are lower than the costs associated to treatment of advanced disease and that cases avoided as a result of early detection, gradually contribute to reduce the health service costs. In addition, the reduction in CRC incidence and mortality causes economic impacts with the potential of interfering in productivity loss.

CRC hospital morbidity and mortality trends can be analyzed to identify the impact of screening, with a view of driving efforts aimed at improving outcomes and reducing costs[20]. CRC screening does not explain the modifications founded in this time series study, mainly because presently there are no governmental programs for population-based CRC screening in Brazil. In addition, even if governmental programs were being planned, it would take a long time to be actually established due to the absence of the necessary infrastructure that requires high technological investments and personnel training.

This is not an easy task and even less so immediate, considering the territorial extension and socioeconomic differences. Therefore, it can only be implemented if it is defined as a priority and all the required resources are correctly identified for the necessary interventions. As a country, we cannot ignore that year after year the number of people, mostly elderly individuals, occupying hospital beds and dying of CRC is increasing, despite this being a preventable disease.

CONCLUSION

In the studied period, it was observed a rising trend in CRC incidence and mortality in Brazil from 2002 to 2016, with higher mortality rates founded in elderly patients.

In general, women (52.1%) were more affected than men, but CRC mortality rates were higher for men aged 60 years and over. Regional disparities were evident, with almost 80% of the deaths occurring in the South and Southeast regions, the mortality rates presented a higher annual increase in the South region and lower values in the Northeast region.

Corroborating mortality data, a rising trend was evidenced in CRC hospital morbidity. The hospitalization rates were similar in both sexes aged ≤60 years and higher for men at advanced ages. South and Southeast presented a higher annual increase in hospitalization rates due to this disease.

The use of secondary data does bring limitations to this study regarding the quality and coverage of the information on causes of death and hospitalization diagnosis. Nevertheless, data does not improve per se. It needs to be used and interpreted. The information generated herein can be used as the basis for the review of prevention and control strategies of this disease.

Authors' contribution

Dominguez RGS contributed to the conception, design, implementation of the research and acquisition of data; to the analysis of the results and to the writing of the manuscript. Participated in drafting the article, gave final approval of the version to be submitted and any revised version.

Bierrenbach AL made substantial contributions to conception and design, acquisition of data, analysis and interpretation of data. Participated in revising the article critically for important intellectual content and gave final approval of the version to be submitted and any revised version.

Orcid

Ramona Garcia Souza Dominguez: 0000-0002-3131-3953.
Ana Luiza Bierrenbach: 0000-0002-6837-0636.

Dominguez RGS, Bierrenbach AL. Morbidade hospitalar e mortalidade por câncer colorretal: implicações para a saúde pública no Brasil. Arq Gastroenterol. 2020;57(2):182-7.

RESUMO – **Contexto** – O câncer colorretal é um grave problema de saúde pública e um dos tipos mais comuns de câncer no mundo. Diferentes tendências têm sido observadas nos países ao redor do mundo. Enquanto as taxas de incidência e mortalidade por câncer colorretal apresentam tendência crescente em países em desenvolvimento, essas taxas têm se mantido em tendência decrescente nos países mais desenvolvidos. **Objetivo** – Analisar a tendência temporal de morbimortalidade por câncer colorretal no Brasil, entre 2002 e 2016. **Métodos** – Pesquisa descritiva de série temporal. Os dados foram extraídos dos sistemas nacionais de informação de Internações Hospitalares e Mortalidade, nos anos respectivos. **Resultados** – Observou-se tendência crescente da morbidade hospitalar e mortalidade por câncer colorretal em todas as regiões do país, constatando-se que morrem mais idosos em idade avançada. As mulheres (52,1%) foram mais acometidas do que os homens, porém as taxas de óbito foram maiores para o sexo masculino a partir dos 60 anos de idade. As disparidades regionais ficaram evidentes, sendo que quase 80% das mortes ocorreram nas regiões Sul e Sudeste, com maior incremento anual na região Sul e menor na região Norte. Em relação à hospitalização, Sul e Sudeste apresentaram maior crescimento anual. **Conclusão** – Os dados agregam conhecimento sobre o perfil das hospitalizações públicas e mortes, reafirmando que o câncer colorretal contribui para uma importante carga de doença e mortalidade no Brasil. Esses elementos trazem implicações para a revisão das estratégias de prevenção e controle do câncer colorretal, bem como para os investimentos na saúde pública.

DESCRITORES – Neoplasias colorretais, mortalidade. Morbidade. Saúde pública. Oncologia.

REFERENCES

1. Instituto Nacional de Câncer (INCA). Estimativa 2018. Brasília (DF); 2018. 124p. [Internet]. [Accessed 2019 Nov 12]. Available from: https://portaldeboaspraticas.iff.fiocruz.br/wp-content/uploads/2019/10/estimativa-incidencia-de-cancer-no-brasil-2018.pdf
2. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68:394-424.
3. Ait Ouakrim D, Pizot C, Boniol M, Malvezzi M, Boniol M, Negri E, et al. Trends in colorectal cancer mortality in Europe: retrospective analysis of the WHO mortality database. BMJ, 2015;351:h4970.
4. Weir HK, Li C, Henley SJ, Joseph D. Years of life and productivity loss from potentially avoidable colorectal cancer deaths in U.S. counties with lower educational attainment (2008–2012). Cancer Epidemiol Biomarkers Prev. 2017;26:736-42.
5. Epidemiology and Information Coordination (CEInfo). Colorectal cancer screening: a challenge to be faced. [Internet] Sao Paulo: Municipal Health Secretary, 2012. [Internet]. [Accessed 2019 June 23]. Available from: https://www.prefeitura.sp.gov.br/cidade/secretarias/upload/saude/arquivos/publicacoes/Boletim_CEInfo_Analise_06.pdf
6. Welch HG, Robertson DJ. Colorectal cancer on the decline - why screening can't explain it all. N Engl J Med. 2016; 374:1605-7.
7. Brasil. Ministério da Saúde. Secretaria de Vigilância em Saúde. Departamento de Vigilância de Doenças e Agravos não Transmissíveis e Promoção da Saúde. Saúde Brasil 2018: Uma análise da situação de saúde e das doenças e agravos crônicos: desafios e perspectivas. Brasilia (DF): Ministério da Saúde, 2019. 424p. [Internet]. [Accessed 2019 June 12]. Available from: http://bvsms.saude.gov.br/bvs/publicacoes/saude_brasil_2018_analise_situacao_saude_doencas_agravos_cronicos_desafios_perspectivas.pdf
8. Saracci R, Wild CP. International Agency for Research on Cancer: the First 50 Years. Lyon, France: International Agency for Research on Cancer; 2015. 259p. [Internet]. [Accessed 2019 December 12]. Available from: https://publications.iarc.fr/Non-Series-Publications/The-History-Of-Iarc/International-Agency-For-Research-On-Cancer-The-First-50-Years-1965–2015
9. Raine R, Wong W, Scholes S, Ashton C, Obichere A, Ambler G. Social variations in access to hospital care for patients with colorectal, breast, and lung cancer between 1999 and 2006: retrospective analysis of hospital episode statistics. BMJ. 2010;340:b5479–b5479.
10. Victora CG, Barreto ML, do Carmo Leal M, Monteiro CA, Schmidt MI, Paim J, et al. Health conditions and health-policy innovations in Brazil: the way forward. Lancet. 2011;377:2042-53.
11. Pagotto V, Silveira EA, Velasco WD. The profile of hospitalizations and associated factors among elderly users of the Brazilian Unified Health System (SUS). Ciência& Saúde Coletiva, 2013;18:3061-70.
12. Mikkelsen L, Phillips DE, AbouZahr C, Setel PW, de Savigny D, Lozano R, et al. A global assessment of civil registration and vital statistics systems: Monitoring data quality and progress. Lancet. 2015;386:1395-406.
13. Lima EEC, Queiroz BL. Evolution of the deaths registry system in Brazil: associations with changes in the mortality profile, under-registration of death counts, and ill-defined causes of death. Cad Saude Publica. 2014;30:1721-30.
14. França EB, Teixeira R, Ishitani L, Duncan BB, Cortez-Escalante JJ, Morais NOL, et al. Ill-defined causes of death in Brazil: a redistribution method based on the investigation of such causes. Rev Saude Publica. 2014;48:671-81.
15. Machado JP, Martins M, Leite IC. Quality of hospital databases in Brazil: some elements. Rev Bras Epidemiol. 2016;19:567-81.
16. Ministry of Health (Brazil). Ministerial ordinance no. 2,439 of December 8th, 2005. Establishes the National Cancer Care Policy: Promotion, Prevention, Diagnosis, Treatment, Rehabilitation and Palliative Care, to be implemented in all federated units, respecting the competences of the three management spheres. Official Diary of the Federative Republic of Brazil. Brasilia (DF), December 9th, 2005; Section 1, p.80-1.
17. Brasil. Ministério da Saúde. Department of Informatics at SUS (DATASUS). In: The National Database on Health Units (CNES) [Internet]. [Accessed 2018 December 23]. Available from: http://cnes.datasus.gov.br/Mod_Hospitalar.asp?VCom.
18. Federal Court of Audit (TCU). Operational Audit Report: National Oncology Care Policy. 2011. [Internet]. [Accessed 2019 December 23]. Available from: https://portal.tcu.gov.br/lumis/portal/file/fileDownload.jsp?inline=1&fileId=8A8182A14D6E85DD014D7327C1CB5497.
19. Brasil. Ministério da Saúde. Department of Health Care, Department of Primary Care. Screening. Brasilia (DF): Ministry of Health; 2013. 95p. [Internet]. [Accessed 2019 June 23]. Available from: http://bvsms.saude.gov.br/bvs/publicacoes/rastreamento_caderno_atencao_primaria_n29.pdf
20. Shieh Y, Eklund M, Sawaya GF, Black WC, Kramer BS, Esserman LJ. Population-based screening for cancer: hope and hype. Nat Rev Clin Oncol. 2016;13:550-65.

ORIGINAL ARTICLE

AG-2020-09
doi.org/10.1590/S0004-2803.202000000-36

Prevalence and factors associated with constipation in premenopausal women: a community-based study

Amanda Almeida Gomes **DANTAS**[1], Isabelle Ribeiro **BARBOSA**[1], Shamyr Sulyvan de **CASTRO**[2], Caroline Wanderley Souto **FERREIRA**[3], Saionara Maria Aires da **CAMARA**[1] and Diego de Sousa **DANTAS**[1,3]

Received: 28 January 2020
Accepted: 26 March 2020

ABSTRACT – **Background** – Intestinal constipation is characterized by problems related to evacuation, and presents high prevalence in the female gender. This condition has demonstrated negative effects on the development of daily activities, causing damage to the physical and emotional well-being of individuals who are diagnosed with it. Studies that investigate what health impairments intestinal constipation can cause are scarce in the literature. **Objective** – This study aimed to verify the prevalence and factors associated with intestinal constipation in premenopausal women living in Northeastern Brazil. **Methods** – It is a cross-sectional study. This was carried out in the northeast of Brazil. Participated 195 women, adult and middle age. Social conditions, habits and lifestyle, clinical aspects and obstetric history were investigated. Constipation was diagnosed using the Rome III Criteria. Multivariate analysis was conducted using Poisson Regression with robust variance to analyze the relationship between intestinal constipation and independent variables. A statistical significance level of $P<0.05$ was considered. **Results** – Most of the women were between 25 and 39 years old (49.2%) and had an income of up to one minimum wage (79.5%). The intestinal constipation prevalence was 35.4%. In the final multivariate regression model, hemorrhoid clinical aspects ($P=0.01$), pain ($P=0.001$) and a burning sensation ($P=0.01$) on bowel movement, and sexual dysfunction ($P=0.03$) remained associated with constipation. **Conclusion** – The present study found a significant prevalence of constipation among premenopausal women and clinical factors such as hemorrhoids, pain and a burning sensation, and sexual dysfunction were associated with intestinal constipation.

HEADINGS – Constipation. Women's health. Premenopause. Epidemiology.

INTRODUCTION

According to the World Gastroenterology Organization[1], intestinal constipation (IC) is characterized by a constant complication to perform bowel movements, incomplete bowel movements, as well as infrequent bowel movements, which are present every 3 or 4 days, or less frequently, and in the absence of alarming symptoms or secondary factors.

Constipation is a common, expensive and costly condition for health services[2], with an estimated worldwide prevalence ranging from 1% to 80% due to the geographical and methodological divergences of the studies. Overall, the average prevalence of constipation in adults has been estimated at 16% worldwide, while reaching 34% among older adults[3,4], and with females being more prone to this condition[5,6].

Women have estrogen and progesterone-related biological issues that directly interfere with gastrointestinal motility through activation of the autonomic nervous system, which may lead to developing constipation[7].

Through a systematic review, Belsey[8] reported that constipation compromises people's quality of life in physical and mental health aspects, and that the impact of IC on adults is similar to that noted in conditions which can be estimated to be more "severe" such as osteoarthritis, rheumatoid arthritis, chronic allergies, and diabetes.

In this context, the importance of investigating the prevalence and factors associated with IC in women is emphasized so that recent epidemiological data can assist researchers and professionals in health promotion and preventing this condition, as there is a gap in scientific knowledge about this outcome. Thus, this study aims to analyze the prevalence and factors associated with intestinal constipation in premenopausal women living in a municipality in northeast Brazil.

METHODS

This is a cross-sectional study conducted in the urban territory of Santa Cruz-RN from December 2015 to November 2016. The research protocol was submitted and approved by the local Research Ethics Committee at Federal University of Rio Grande do Norte under the CAAE number: 49237315.9.0000.5568. The study was conducted in line with the terms of the Declaration of Helsinki.

Declared conflict of interest of all authors: none
Disclosure of funding: no funding received
[1] Universidade Federal do Rio Grande do Norte, Faculdade de Ciências da Saúde de Trairi (FACISA), Santa Cruz, RN, Brasil. [2] Universidade Federal do Ceará, Fortaleza, CE, Brasil. [3] Universidade Federal de Pernambuco, Recife, PE, Brasil.
Corresponding author: Diego de Sousa Dantas. E-mail: diegodantas1@gmail.com

Santa Cruz is a small city with low economic potential located in the interior of Northeastern Brazil, in the rugged interior Potiguar (RN) region with 38,538 inhabitants and an area of 624.356 km. The municipality has health coverage of 97.83% by the Family Health Program (PSF). In this sample, 11,736 inhabitants are women of reproductive age aged between 10 and 49 years, representing 30.45% of the total resident population in this location[9].

The sample size calculation considered a prevalence of 36.9% of constipation in women[10], a relative error of 20% and a non-response rate of 15%, resulting in a sample of 194 participants.

The sample composition was performed by proportional stratified sampling based on the health territories assigned to the family health units of the municipality and women were recruited through an active search.

The study included women of reproductive age (19 and 49 years old), non-pregnant women with regular menstrual cycle and who agreed to participate by signing the informed consent form. Women with cognitive impairment which prevented applying questionnaires or who did not finalize the research protocol would have been excluded, however no participants were excluded in the present study. Pregnant women were not included as it is known that the risk of constipation is high during pregnancy due to the significant increase in sex hormones, reduced bowel movement and emptying due to mechanical compression caused by the placenta[4].

Data collection was performed by previously trained interviewers in their own health units. The participants were invited to this study while waiting for habitual appointment. The participants answered questions about hers life and the Rome III Criterion[11], considered the gold standard, to define the dependent study variable, which was IC. The same instrument was used as data collection began in December 2015, as the Rome IV criterion had not yet been published. This instrument was applied in a room available in each health unit, seeking to preserve or confidentiality of the data collected. It is worth noting that no woman refused or gave up to collaborate with this research.

The Rome III criterion is a collective product of committees and medical societies developed by experts in the field, and refers to a uniform instrument for making the most accurate IC diagnosis. According to this criterion, the symptoms for diagnosing constipation must start six months before the evaluation, and must be active for at least three months in at least one quarter of the bowel movements, and the individual must have two or more symptoms from the questionnaire's own list, including: a) less than three bowel movements per week, b) straining when evacuating, c) the presence of hard or broken stools, d) feeling of incomplete bowel movement, e) feeling of anorectal block, and f) manual maneuvers to facilitate evacuations[11].

The analyzed independent variables involved questions related to: a) population characterization: age group, which was grouped according to life cycle, namely: young adult (19 to 24 years old), adult (25 to 39 years old) and middle aged (40 to 49 years); marital status, which was dichotomized into with and without a partner; ethnicity, grouped in white and others; education, which was considered until elementary school and high school or higher; and income, which was grouped up to 1 minimum monthly salary and >1 minimum monthly salary; b) lifestyle: physical inactivity and self-rated of health dichotomized into poor (bad or very bad) and good (regular, good and very good) health; c) clinical aspects, measured by self-report: hemorrhoids, pain during evacuation, pruritus ani, presence of blood in the stool and burning sensation during the bowel movement; and d) reproductive history, which included types of delivery, episiotomy, dysmenorrhea and sexual dysfunction.

Physical inactivity was assessed through the short version of the IPAQ – International Physical Activity Questionnaire[12], validated for the Brazilian population. IPAQ quantifies energy expenditure in METs-minute/week with physical activity. Women with lower values <600 METs-minute/week are considered sedentary[13].

Self-rated health was assessed using the five-point likert scale for the question "How do you rate your health at this time?", being categorized as: fair, good, very good, bad and very bad[14].

Sexual dysfunction was assessed by the Female Sexual Quotient (FSQ)[15]. This questionnaire assesses various domains of women's sexual activity. Women with a score of 60 points or less were considered as having sexual dysfunction, according to the cut-off point established for screening for dysfunction[16].

Data were tabulated and analyzed using the Statistical Package for Social Sciences (SPSS) version 22.0 software. Descriptive and inferential statistics were employed for data analysis. Bivariate analysis was performed using the chi-squared test. Poisson regression with robust variance was used to estimate gross and adjusted prevalence ratios (PR) of intestinal constipation and to calculate the respective confidence interval (95% CI). Variables with significant association ($P \leq 0.20$) were included in the multivariate model in the bivariate analysis for the crude PR analysis, and only those variables that had statistical significance of ($P \leq 0.05$) were included in the adjusted model. The Multivariate analysis was conducted using Poisson regression with robust variance.

RESULTS

There were 195 women included in the study and the prevalence of constipation was 35.4%.

In the bivariate analysis, the clinical variables hemorrhoids (P=0.03), pain during evacuation (P=0.001), pruritus ani (P=0.03), presence of blood in the stool (P=0.001), burning sensation during evacuation (P=0.001), dysmenorrhea (P=0.05) and sexual dysfunction (P=0.02) were associated with constipation. The sociodemographic and lifestyle variables did not present a statistically significant difference between the groups (TABLE 1).

Through multivariate analysis it was observed that the variables pain (P=0.001) and burning during evacuation (P=0.01), hemorrhoids (P=0.01) and sexual dysfunction (P=0.03) remained associated to CI (TABLE 2).

DISCUSSION

When analyzing the prevalence and factors associated with constipation in adult women living in a municipality in the interior of Northeastern Brazil, a prevalence of 35.4% was found to be associated with clinical factors, such as the presence of hemorrhoids, pain and burning during bowel movement, and sexual dysfunction. Other investigated variables such as age, physical inactivity, education and obstetric factors were not associated with this condition.

In Brazil, Schmidt and Santos[17] found an estimated IC prevalence of 16% in their study in the city of Londrina, and women were the most affected with frequencies which varied by self-report and by the Rome III Criteria of between 21% to 24% compared with men whose prevalence ranged from 4% to 6%. In another population-based study which investigated IC prevalence and associated

TABLE 1. Bivariate analysis of study population characterization, lifestyle, clinical aspects and obstetric history of adult women. Santa Cruz, Rio Grande do Norte, Brazil – 2016.

	Constipação – 35.4%				*P* value
	Yes (n=69)		No (n=126)		
	n	%	n	%	
Age					
Young adult (19 to 24 years old)	15	21.7	25	19.8	0.94
Adult (25 to 39 years old)	33	47.8	63	50.0	
Middle aged (40 until 49 years old)	21	30.5	38	30.2	
Ethnicity					
White	20	29.0	38	30.2	0.86
Others	49	71.0	88	69.8	
Education					
Until elementary school	32	46.4	61	48.4	0.79
High school or higher	37	53.6	65	51.6	
Income					
Up to 1 minimum monthly salary	57	82.6	98	77.8	0.42
>1 minimum monthly salary	12	17.4	28	22.2	
Marital status					
Without partner	27	39.1	64	50.8	0.12
With partner	42	60.9	62	49.2	
Physical inactivity					
Yes	10	14.5	29	23.0	0.16
No	59	85.5	97	77.0	
Self-rated of health					
Good	48	69.6	97	77.0	0.26
Poor	21	30.4	29	23.0	
Hemorrhoids					
Yes	10	14.5	4	3.2	0.03*
No	59	85.5	122	96.8	
Pain during evacuation					
Yes	32	46.4	6	4.8	0.001*
No	37	53.6	120	95.2	
Pruritus ani					
Yes	4	5.8	1	0.8	0.03*
No	65	94.2	125	99.2	
Presence of blood in the stool					
Yes	16	23.2	2	1.6	0.001*
No	53	76.8	124	98.4	
Burning sensation during evacuation					
Yes	18	26.1	0	0	0.001*
No	51	73.9	126	100.0	
Cesarean					
Yes	26	37.7	52	41.3	0.62
No	43	62.3	74	58.7	
Vaginal delivery					
Yes	36	52.2	55	46.7	0.25
No	33	47.8	71	56.3	
Episiotomy					
Yes	17	24.6	39	31.0	0.35
No	52	75.4	87	69.0	
Dysmenorrhea					
Yes	45	65.2	64	50.8	0.05*
No	24	34.8	62	49.2	
Sexual disfunction					
Yes	32	46.4	38	30.2	0.02*
No	37	53.6	88	69.8	

* *P*-value<0.05. *P*-value calculate by chi-square test.

TABLE 2. Multivariate analysis of clinical and obstetric aspects of adult women. Santa Cruz, Rio Grande do Norte, Brazil – 2016.

	PR crude	95%CI	*P* value	PR adjusted	95%CI	*P* value
Pain during evacuation						
Yes	3.95	2.76–5.65	0.001*	2.76	1.90–4.06	0.001*
No	1.00			1		
Burning sensation during evacuation						
Yes	3.60	2.75–4.72	0.001*	1.64	1.17–2.31	0.01*
No	1.00			1		
Hemorrhoids						
Yes	2.22	1.48–3.35	0.001*	1.93	1.16–3.20	0.01*
No	1.00			1		
Sexual disfunction						
Yes	1.52	1.04–2.21	0.03*	1.45	1.04–2.04	0.03*
No	1			1		
Dysmenorrhea						
Yes	1.16	1.02–1.32	0.03*	1.32	0.91–1.91	0.14
No	1			1		
Presence of blood in the stool						
Yes	1.73	0.82–3.63	0.15			
No	1					
Pruritus ani						
Yes	1.91	0.84–4.35	0.12			
No	1					

PR: prevalence ratio. Akaike Information Criteria (AIC): 256.37 Model Adjustment (x^2): *P*=0.001.

factors in adults in the city of Pelotas-RS, the authors identified a prevalence of 25.6% of constipation through self-report and 26.9% through using the Rome Criteria III. The prevalence of IC was 2.5 times also more frequent in women (36.9%) than in men (14%) in this study[10]. However, there are no official statistics in Brazil, nor studies in other regions of the country. The National Health Policy (PNS), for example, does not raise questions about this theme[18].

Biomechanical aspects involved in bowel movement may contribute to a higher prevalence of constipation in women, such as pelvic floor muscle and nerve injury which may occur during vaginal delivery, for example[19]. Alterations in the pelvic floor muscles predispose to problems such as urinary incontinence, sexual dysfunction and constipation. Impaired pelvic floor function is believed to be one of the factors which may explain the association between constipation and sexual dysfunction, which may explain the outcome of this study[20]. There are few studies in the literature evaluating the impacts of constipation on sexual function. However, a recent review[21] shows that early evidence suggests that IC is associated with difficulties in female sexual function.

In the present study, 79.5% of participants have a monthly family income of up to one minimum monthly salary. Although income was not a variable associated with IC prevalence, there is previous evidence in the literature of an increased constipation prevalence associated with low socioeconomic status[22,23]. This is perhaps explained by the influence of social standards in favoring higher risk behavior such as poor diet and physical inactivity in individuals from disadvantaged classes[24].

The association of hemorrhoids and pain and burning during evacuation identified in this study are explained by the pathophysiology of intestinal constipation itself[25]. Functional defeca-

tion disorders are associated with many factors, including rectal hypersensitivity, altered rectal reflex activity, increased rectal duct capacity, and rectal motor dysfunction[3], and are associated with a fear of defecating pain due to the presence of bulky or hard stools, hemorrhoids and anal fissure[25].

Riss et al.[26] claim that little is known about the connection between hemorrhoids and anorectal function. The authors describe that complaints such as pain, effort and need for evacuation stimulation is common in constipated patients (laxatives, finger maneuvers or enemas) and expressed significant correlation with the presence of hemorrhoids, and this is because there are varicose veins present in the rectum which can be aggravated by exertion during bowel movements. In their study, these authors observed that individuals with a higher degree of hemorrhoids showed an increase in constipation symptoms.

On the other hand, the presence of pain and burning during bowel movements is mainly related to stool consistency, which leads to excessive, prolonged and sometimes unsatisfactory defecatory effort, causing the individual to perform finger or manual maneuvers to be able to expel the stool[1].

Del' Arco[27] found in their study that gastrointestinal diseases, including constipation, negatively impact different elements of quality of life in Brazilian women, such as mood, concentration and sexuality, so studying the prevalence and correct management of this condition is important. Thus, this study seeks to contribute by identifying factors which are related to IC and to support planning actions aimed at patients suffering from constipation through these findings, thus improving the care provided by health professionals.

Physical inactivity in this study was not associated with the IC prevalence, and this may have happened because only physical activity was evaluated, not physical exercise. However, physical activity and proper nutrition appear as important actions to regulate gastrointestinal motility, as a high-fiber diet can increase stool weight, resulting in a shorter colon transit time, while a low-fiber diet leads to constipation[27], while physical activity can increase propulsion movements in the large intestine[28].

No association of constipation with age was observed. This may be due to the fact that the studied sample was only composed of adult women. The literature shows a difference between the group of young and older individuals, but this population was not investigated in this study[29].

As limitations of this work, we highlight the cross-sectional design which limits interpreting the data to associations, susceptible to reverse causality, and also precludes a better understanding of the phenomenon due to the impossibility of establishing causality[30]. Another limitation may be related to clinical aspects relevant to understanding IC such as anthropometric data, body composition, and body water percentage, but not included in this study due to the logistical difficulty to measure variables in epidemiological studies. In addition, inaccurate questionnaires such as IPAQ were used. As the study was developed from a population in a small town, other studies with methodological designs more representative of the Brazilian population are encouraged.

CONCLUSION

There are high prevalence of constipation between adult and middle age women. Clinical factors like hemorrhoids, pain and burning sensation during evacuation, and sexual dysfunctions are associated with constipation. Sociodemographic factors and life habits as physical activity did not associated with this condition.

Authors' contribution

AAG Dantas: conceptualization, data curation, formal analysis, writing–original draft and review & editing; IR Barbosa: data analysis and writing–original draft; SS Castro: writing–original draft and review & editing; SMA Camara: writing–original draft and review & editing; DS Dantas: conceptualization, supervision, data curation, formal analysis, writing–original draft and review & editing.

Orcid

Amanda Almeida Gomes Dantas: 0000-0002-7621-086X.
Isabelle Ribeiro Barbosa: 0000-0002-1385-2849.
Shamyr Sulyvan de Castro: 0000-0002-2661-7899.
Caroline Wanderley Souto Ferreira: 0000-0003-2736-5918.
Saionara Maria Aires da Camara: 0000-0002-3054-7213.
Diego de Sousa Dantas: 0000-0002-1966-3352.

Dantas AAG, Barbosa IR, Castro SS, Ferreira CWS, Camara SMA, Dantas DS. Prevalência e fatores associados à constipação em mulheres na pré-menopausa: um estudo de base comunitária. Arq Gastroenterol. 2020;57(2):188-92.

RESUMO – **Contexto** – A constipação intestinal é caracterizada por problemas relacionados à evacuação, e apresenta alta prevalência no gênero feminino. Essa condição tem demonstrado efeitos negativos no desenvolvimento das atividades diárias, causando prejuízos no bem-estar físico e emocional dos indivíduos que são diagnosticados com ela. Estudos que investiguem quais prejuízos à saúde a constipação intestinal pode ocasionar são escassos na literatura. **Objetivo** – Este estudo teve como objetivo verificar a prevalência e os fatores associados à constipação intestinal em mulheres na pré-menopausa residentes no nordeste do Brasil. **Métodos** – Estudo transversal realizado no Nordeste do Brasil. Participaram 195 mulheres adultas e de meia idade. Condições sociais, hábitos e estilo de vida, aspectos clínicos e história obstétrica foram investigados. A constipação foi diagnosticada através dos Critérios de Roma III. A análise multivariada foi conduzida através da Regressão de Poisson com variância robusta, para analisar a relação entre constipação intestinal e variáveis independentes. Considerou-se o nível de significância estatística de $P \leq 0,05$. **Resultados** – A maioria das mulheres estava na faixa etária de 25 a 39 anos (49,2%) e possuía renda de até um salário mínimo (79,5%). A prevalência da constipação intestinal foi de 35,4%. No modelo final da regressão multivariada, os aspectos clínicos hemorroidas ($P<0,01$), dor ($P<0,001$) e ardor ($P<0,01$) ao evacuar e disfunção sexual ($P<0,03$) permaneceram associados à constipação. **Conclusão** – O presente estudo encontrou uma prevalência significativa de constipação entre mulheres na pré-menopausa e fatores clínicos como hemorroidas, dor e ardor na evacuação, e disfunção sexual se associaram a constipação intestinal.

DESCRITORES – Constipação intestinal. Saúde da mulher. Pré-Menopausa. Epidemiologia.

REFERENCES

1. WGO. World Gastroenterology Organisation Practice Guidelines. Constipação: uma perspectiva mundial. Novembro, 2010.
2. Sun SX, Dibonaventura M, Purayidathil FW, Wagner JS, Dabbous O, Mody R. Impact of chronic constipation on health-related quality of life, work productivity and health resource use: an analysis of the National Health and Welfare Survey. Dig Dis Sci. 2011;56:2688-95.
3. Sanchez MI, Bercik P. Epidemiology and burden of chronic constipation. Can J Gastroenterol. 2011;25 (Suppl B):11B-15B.
4. Forootan M, Bagher N, Darvishi M. Chronic constipation A review of literature. Medicine (Baltimore). 2018;97:e10631.
5. Iraji N, Keshteli AH, S Sadeghpour, Daneshpajouhnejad P, Fazel M, Adibi P. Constipation in Iran: SEPAHAN Systematic Review No 5. Int J Prev Med. 2012;3(Suppl 1):S34-41.
6. Sommers T, Mitsuhashi S, Singh P, Hirsch W, Katon J, Ballou S, et al. Prevalence of Chronic Constipation and Chronic Diarrhea in Diabetic Individuals in the United States. Am J Gastroenterol. 2019;114:135-42.
7. Ji-Eun Oh, Yong-Woon Kim, Parque So-Young, Jong-Yeon Kim. Estrogen, instead of progesterone, causes constipation in female and male mice. Coreano J Physiol Pharmacol. 2013;17:423-6.
8. Belsey J, Greenfield S, Candy D, Geraint M. Systematic review: Impact of constipation on quality of life in adults and children. Aliment Pharmacol Ther. 2010;31:938-49.
9. Instituto Brasileiro de Geografia e Estatística. Cidades@. [Internet] [Access 2014 November] Available from: http://www.cidades.ibge.gov.br/xtras/perfil.php?lang=&codmun=2411.
10. Collete VL, Araújo CL, Madruga SW. Prevalência e fatores associados à constipação intestinal: um estudo de base populacional em Pelotas, Rio Grande do Sul, Brasil. Cad Saúde Pública. 2010;26:1391-402. Doi: 10.1590/S0102-311X2010000700018
11. Longstreth GF, Thompson WG, Chey WD, Houghton LA, Mearin F, Spiller RC. Functional bowel disorders. Gastroenterology. 2006;130:1480-91.
12. IPAQ Research Committee. Guidelines for Data Processing and Analysis of the International Physical Activity Questionnaire (IPAQ). International Physical Activity Questionnaire (IPAQ). 2005;1-15.
13. Pardini R, Matsudo SM, Araújo, T, Matsudo V, Andrade E, Braggion G. Validação do questionário internacional de nível de atividade física (IPAQ - versão 6): estudo piloto em adultos jovens brasileiros. Rev Bras Ciên e Mov. 2001;9:45-51.
14. Dawes J. Do data characteristics change according to the number of scale points used? An experiment using 5-point, 7-point and 10-point scales. International Journal of Market Research. 2008;50:61-77.
15. Abdo CHN. Quociente sexual feminino: um questionário brasileiro para avaliar a atividade sexual da mulher. Diagn Tratamento. 2009;14:89-1.
16. Abdo CHN. Elaboração e validação do quociente sexual – versão feminina, uma escala para avaliar a função sexual da mulher. RBM Rev Bras Med. 2006;63:477-82.
17. Schmidt FMQ, Santos VLCG, Domansky RC, Barros E, Bandeira MA, Tenório MAM, Jorge JMN. Prevalence of self-reported intestinal constipation in adults of the general population. Rev Esc Enferm USP. 2015;49:440-9.
18. Instituto Brasileiro de Geografia e Estatística. Pesquisa Nacional de Saúde. [Internet] 2013. [Access 2019 January] Available from: <http://www.ibge.gov.br/home/presidencia/noticias/imprensa/ppts/00000014100108112013015712834 36.pdf>.
19. Fradet M, Deparis C, Gachon J, Sichitiu B, Pierre J, Frite F, Desseauve D. Lesions and symptoms of the obstetric anal sphincter after subsequent deliveries: a study of 60 patients. Eur J Obstet Gynecol Reprod Biol. 2018;222:40-6.
20. Goa G, Ding S, Ding Y, Jin X, Chen Q, Zhou H, et al. Distribution of the symptoms of patients with female pelvic floor dysfunction with constipation as the main complaint. Zhonghua Wei Chang Wai Ke Za Zhi. 2018;21:798-802.
21. Thomas GP, Maeda Y, Vaizey CJ. A review of the effect of faecal incontinence and constipation on sexual function. Int J Colorectal Dis. 2019;34:387.
22. Bytzer P, Howell S, Leemon M, Young LJ, Jones MP, Talley NJ. Low socioeconomic class is a risk factor for upper and lower gastrointestinal symptoms: a population based study in 15,000 Australian adults. Gut. 2001;49:66-72.
23. Shi H, Yao L, Zhou M. Correlation Analysis between Chronic Functional Constipation and Syndrome Caused by Northwest Dryness-evil. Xinjiang Journal of Traditional Chinese Medicine. 2010;(2):5-7. Available from: http://caod.oriprobe.com/articles/23453121/Correlation_Analysis_between_Chronic_Functional_Constipation_and_Syndr.htm
24. Stewart WF, Liberman JN, Sandler RS, Woods MS, Stemhagen A, Chee E, et al. Epidemiology of constipation (EPOC) study in the United States: Relation of clinical subtypes to sociodemographic characteristics. Am J Gastroenterol. 1999;12:3530-40.
25. Alves JG. Constipação Intestinal. JBM. 2013;101:31-7.
26. Riss S, Weiser FA, Schwameis K, Mittlböck M, Stift A. Haemorrhoids, constipation and faecal incontinence: is there any relationship? Colorectal Dis. 2011;13:227-33.
27. Del'arco A, Magalhaes P, Quilici FA. SIM Brasil study women's gastrointestinal health: gastrointestinal symptoms and impact on the Brazilian women quality of life. Arq Gastroenterol. 2017;54:115-22.
28. Moezi P, Salehi A, Molavi H, Hossein Poustchi H, Gandomkar A, Imanieh MH, Malekzadeh R. Prevalence of chronic constipation and its associated factors in the pars cohort study: a study of 9,000 adults in Southern Iran. Middle East J Dig Dis. 2018;10:75-83.
29. Walter S, Hallbook O, Gotthard R, M Bergmark, Sjodahl R. A population-based study of bowel habits in a Swedish community: prevalence of fecal incontinence and constipation. Scand J Gastroenterol. 2002;37:911-26.
30. Fletcher RH, Fletcher SW. Epidemiologia Clínica: elementos essenciais. 4º ed. Porto Alegre: Artmed; 2006.

ORIGINAL ARTICLE

AG-2020-10
doi.org/10.1590/S0004-2803.202000000-37

Underwater endoscopic mucosal resection for non-pedunculated colorectal lesions. A prospective single-arm study

Luciano **LENZ**[1,2], Bruno **MARTINS**[1,2], Fabio Shiguehisa **KAWAGUTI**[1,2], Alexandre **TELLIAN**[3], Caterina Maria Pia Simoni **PENNACHI**[1], Mauricio **SORBELLO**[1,3], Carla **GUSMON**[1], Gustavo Andrade de **PAULO**[1,4], Ricardo **UEMURA**[1], Sebastian **GEIGER**[1], Marcelo Simas de **LIMA**[1], Adriana **SAFATLE-RIBEIRO**[1,3,5], Elisa **BABA**[1], Claudio Lyoiti **HASHIMOTO**[3,5], Fauze **MALUF-FILHO**[1] and Ulysses **RIBEIRO JR**[1]

Received: 28 January 2020
Accepted: 27 March 2020

ABSTRACT – **Background** – Underwater endoscopic mucosal resection (UEMR) has emerged as a revolutionary method allowing resection of colorectal lesions without submucosal injection. Brazilian literature about this technique is sparse. **Objective** – The aim of this study was evaluate the efficacy and safety of UEMR technique for removing non-pedunculated colorectal lesions in two Brazilian tertiary centers. **Methods** – This prospective study was conducted between June 2016 and May 2017. Naïve and non-pedunculated lesions without signs of submucosal invasion were resected using UEMR technique. **Results** – A total of 55 patients with 65 lesions were included. All lesions, except one, were successfully and completely removed by UEMR (success rate 98.5%). During UEMR, two cases of bleeding were observed (3.0%). One patient had abdominal pain on the day after resection without pneumoperitoneum. There was no perforation or delayed bleeding. **Conclusion** – This study supports the existing data indicating acceptable rates of technical success, and low incidence of adverse events with UEMR. The results of this Brazilian study were consistent with previous abroad studies.

HEADINGS – Intestinal polyps. Colorectal neoplasms. Endoscopic mucosal resection. Immersion. Prospective studies.

INTRODUCTION

Colorectal cancer is a leading cause of cancer mortality worldwide[1]. The endoscopic removal of polyps reduces the incidence of colorectal cancer by up to 90%[2]. Ninety percent of polyps are small and can be easily treated with conventional polypectomy[3]. However, larger non-pedunculated lesions pose a technical challenge[2].

Advanced endoscopic therapeutic options for colorectal lesions have been developed. Conventional endoscopic mucosal resection (CEMR) is the current accepted standard modality. CEMR utilizes submucosal injection of a solution to separate the superficial layers from the deep submucosa and the muscularis propria[4]. Theoretically, it decreases the risk of thermal injury to the deeper tissue layers and iatrogenic perforation. However, submucosal injection may paradoxically make snare capture of a flat polyp more difficult[5].

An alternative technique, endoscopic submucosal dissection (ESD), has also been developed to remove lesions that were previously removed only by surgical means. This technique has the ability to obtain en bloc resection of large lesions, but it is complex, technically demanding and time consuming. In addition, ESD is associated with high risk of perforation and has a long learning curve[4].

Developed by Binmoeller et al.[5] in 2012, and later described as the "third way" by Amato et al.[6], underwater endoscopic mucosal resection (UEMR) has emerged as a revolutionary method allowing resection without submucosal injection. Recent studies demonstrated that UEMR safely removes large lesions due to natural separation of the submucosa from the muscularis propria when air insufflation is not used. Additionally, they showed high technical success with few adverse events[1,4-13].

The overwhelming majority of studies have been published about overseas UEMR experience[1,4-14]. Only two South American studies, both Brazilian, were published regarding the underwater technique for colorectal lesions. The first Brazilian study included four patients, one with a pedunculated lesion[13]. The other one included 14 lesions, all of which were sessile serrated adenomas[7].

This prospective single-arm study evaluated the safety and efficacy of a UEMR for removing non-pedunculated colorectal lesions using the snare for marking and using three different electrosurgical settings in two Brazilian referral centers.

METHODS

Patients

Between June 2016 and May 2017, a prospective non-controlled trial was conducted with consecutive patients undergoing UEMR in two university tertiary hospitals. The inclusion criteria were: (1)

Declared conflict of interest of all authors: none
Disclosure of funding: no funding received
[1] Universidade de São Paulo, Faculdade de Medicina, Departamento de Gastroenterologia, Instituto do Câncer do Estado de São Paulo, São Paulo, SP, Brasil. [2] Fleury Medicina e Saúde, São Paulo, SP, Brasil. [3] Universidade de São Paulo, Faculdade de Medicina, Departamento de Gastroenterologia, Divisão de Gastroenterologia e Hepatologia Clínica, Centro de Diagnóstico em Gastroenterologia, São Paulo, SP, Brasil. [4] Hospital Israelita Albert Einstein, Serviço de Endoscopia, São Paulo, SP, Brasil. [5] Hospital Sírio-Libanês, São Paulo, SP, Brasil.
Corresponding author: Luciano Lenz. E-mail: luciano88lenz@gmail.com

non-pedunculated lesions; (2) size between 10 and 40 mm; (3) naïve lesions; (4) no signs of invasive disease (ulceration, spontaneous bleeding, indurations, or non-floating sign). The study protocol was approved in 10th June 2016 by our Institutional Review Board (*Núcleo de Pesquisa*) as a part of a pilot study before a clinical trial comparing CEMR and UEMR (NCT03021135). This study protocol conforms to the ethical guidelines of Helsinki Declaration. A written, informed consent was obtained from all patients included in this study.

METHODS

All procedures were performed on an outpatient basis and under sedation. Miniprobe EUS examination not used. A high definition colonoscope (GIF-H180 or 190, Olympus Medical, Center Valley, Pa) without a distal cap was used. Intravenous hyoscine was administered (if no contra-indications) to arrest peristalsis. The endoscopists, who performed the procedures, learned UEMR watching internet videos, and reading the available articles about the technique, however, they had never performed UEMR before this study.

Two types of snares were used: 13 mm Captivator II® (Boston Scientific, Marlborough, USA) or 25 mm Snare Master® (Olympus, Center Valley, USA). The snare was chosen according to the lesion size and at the discretion of the endoscopist. The electrosurgical unit used was the VIO 300 D (ERBE Elektromeddzin, Tubingen, Germany).

The lesions were examined by white light, virtual chromoscopy (NBI - Narrow Band Image), and conventional chromoscopy (0.4% indigo carmine solution) without magnification. After identifying the target lesion, UEMR was started by marking the perimeter with the tip of snare (soft coagulation, 50–80W) under air insufflation (FIGURE 1). Next, the intestinal lumen was decompressed. The lumen was then filled with room temperature water using an irrigation pump (OFP-2, Olympus). A torque-crimp method was used to maximize tissue ensnaring (FIGURE 2). One of three electrosurgical settings chosen (DRYCUT – effect 5, power 60W; AUTOCUT – effect 5, power 80W or ENDOCUT Q – effect 3, interval cut 6, time cut 1). Adjacent parts of the lesion were resected in a piecemeal way, taking care not to leave any pathological "island". Remnant tissue too small to snare was removed by cold forceps biopsy. Neither argon plasma coagulation nor hot biopsy forceps were used. All specimens were retrieved for histopathological examination. Endoclips were employed for the management of hemorrhage, or according to the operator's judgment, e.g., for deep wounds or in patients with higher risk of bleeding (aspirin use or coagulopathy). The procedure was timed, beginning with the marking of the edges until the resection of the last fragment. Tattooing was done to facilitate localization of the resection site. It was performed 3 cm distal, on the same wall of the lesion after saline bleed with 0.5 mL of India ink.

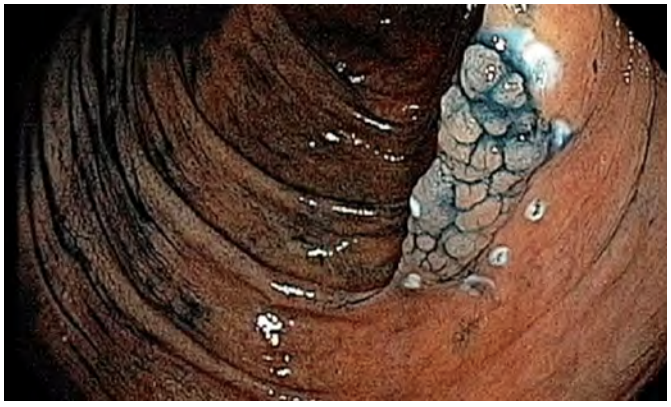


FIGURE 1. Marks made with snare tip.

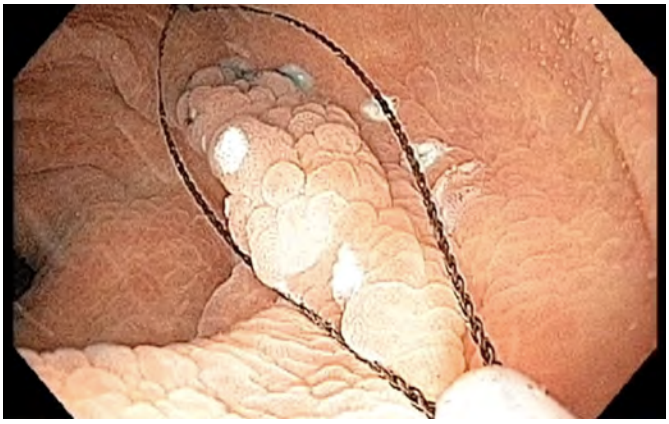


FIGURE 2. Lesion ensnaring underwater.

Follow-up

We called the patients at least 10 days after the procedure to assess delayed adverse events. Surveillance colonoscopies were scheduled 6 months later. The scars were inspected by white light, NBI and conventional chromoscopy followed by biopsies. Recurrences were defined as histologically-proven adenomas at the resection site. We did not consider procedural minimal bleeding without need of intervention as an adverse event. Adverse events were categorized as early (intraprocedural or within 24 hours) or delayed (after one day).

RESULTS

Patient and lesion characteristics

Over 11 months, a total of 55 patients – 34 female (60%), mean age 67 years, range 53–87) with 65 lesions (mean size 16.67 mm, range 10–40 mm) underwent UEMR. The patient and lesion characteristics (gender, age, location, size, morphology, and histopathology) are listed in TABLE 1.

For seven lesions, we selected DRYCUT mode; for sixteen AUTOCUT; and for forty-two the ENDOCUT mode. Forty lesions were removed en bloc (61.5%) and 25 (38.5%) in piecemeal. The procedure time was recorded in 36 lesions (mean time 12 minutes; range 4–40). Of the 65 colorectal lesions, 64 (98.5%) were successfully removed by UEMR (TABLE 2). The exception was a lesion in the sigmoid that was 80% removed by UEMR. However, the remaining part of the lesion was located behind a fold and could not be reached by this route. The submucosal injection was then used, achieving complete resection. Despite buoyancy and adequate elevation with submucosal injection, histopathological examination revealed massive submucosal infiltration (SM3), and the patient was referred for surgical treatment. However, she died due to primary lung cancer before colonic surgery. Two more patients with deep submucosal invasion (SM2) were also referred to colectomy. No

TABLE 1. Patient and lesion characteristics.

Gender (%)	
Male	21 (38.2)
Female	34 (61.8)
Age, y	
Median (range)	67 (53–87)
Total n. of lesions	65
Lesion size, mm	
Median (range)	16.67 (10–40)
Lesion localization n.	
Cecum	7
Ascendending	25
Transverse	11
Descending	8
Sigmoid	6
Rectum	8
Paris classification	
Is	10
II a	44
Is + II a	11
Histology n. (%)	
Sessile serrated	19 (29.2)
Tradicional serrated	1 (1.5)
Tubular adenoma	22 (33.8)
Tubulovillous adenoma	15 (23.1)
Intramucosal carcinoma	4 (6.2)
Submucosal carcinoma	4 (6.2)

TABLE 2. Procedures and outcomes.

Setting – n. of lesions (%)	
Auto cut	16 (24.6%)
Dry cut	7 (10.8)
Endo cut	42 (64.6)
Resection	
En bloc n. (%)	40 (61.5)
Piecemeal n. (%)	25 (38.5)
Procedure time, min*	
Median (range)	12 (4–40)
Success n. (%)	64 (98.5)
Complications	
Total n. of patients	3 (5.4)
Bleeding	2 (3.6)
Post-polypectomy syndrome	1 (1.8)
Perfuration	0
Follow-up, n. patients (%)	41 (74.5)
Mean of follow-up – months (range)	6.8 (1–17)
Residual at follow-up, n. lesions (%)	3 (6)

*Recorded in 36 procedures.

residual cancers were found in the surgical specimens in both cases. Additionally, one patient with superficial submucosal invasion (SM1) could not have endoscopic follow-up due to comorbidities.

During UEMR AUTOCUT mode, spurting bleeding was observed in two patients (5.45%). Hemostasis was easily achieved in both cases by clipping. Neither required blood transfusion. One patient had severe abdominal pain on the day after the procedure, without signs of pneumoperitoneum by tomography. The patient was treated conservatively with antibiotics. There was no delayed hemorrhage or perforation (TABLE 2).

Fourteen patients did not have the endoscopic evaluation for recurrence. Four patients died before the follow-up (one of them with deep SM invasion). The two other patients with deep submucosal invasion (SM2/3) were submitted for surgical treatment. Two additional patients were lost to follow-up. Five patients, due to severe comorbidities, were not in suitable clinical condition to undergo the new colonoscopy. In one patient, the resection site could not be evaluated due to poor bowel preparation. Follow-up colonoscopy was performed in 41 patients (74.54%) with 50 lesions (76.92%). Local recurrence was detected at three resection sites (6%) (TABLE 2). All recurrences were smaller than 5 mm and were easily removed with cold forceps biopsy.

DISCUSSION

Developed by Binmoeller in 2012[5], UEMR is a relatively new technique with few articles published in the literature so far[4-10,12,13,15-17]. In our study, we have shown that UEMR is effective, easy-to-learn and with low risk of adverse events.

Marking the margins is optional. However, it is recommended because sometimes it is more difficult to define the edges underwater. The marks can be made with an argon catheter[5,6] or with the snare tip[1]. In this study we used the snare tip (FIGURE 1), which is kept in the working channel while the lumen is filled with water. In addition, we saved time and resources by replacing the argon catheter with the snare.

Electrosurgical settings are determined by trial and error and personal preference[11]. In the literature, the effect ranged from 2 to 5 and the maximum power, between 30 and 120 W. DRYCUT was the most commonly selected mode[1,5,8,17]. ENDOCUT mode was favored in two studies[6,10], whilst only Binmoeller et al. in 2015 used AUTOCUT setting[12]. In our study, we initially used the DRYCUT mode, but due to the occurrence of minor, non-clinically significant bleeding, we changed to AUTOCUT mode. However, patients in this group had significant bleeding demanding endoscopic management. Finally, we used ENDOCUT mode, which was used for most patients, with no bleeding experienced. Our sample size does not allow conclusions to be drawn as to which mode is safer. However, we suggest, until trials comparing the different modes are performed, that the endoscopist tests the three modes and verifies which one is of his or her preference.

In the literature, the technical success rate is also high (90%–100%)[1,4-14,16]. In the meta-analysis, the pooled resection of UEMR on 508 colorectal lesions was 96.36%[14]. In our study, only one of the 65 lesions (resection rate of 98.5%) was not completely resected by the underwater technique alone. This was a 3 cm lesion in the sigmoid, the most distal part of which was resected underwater. The remainder of the lesion was then completely removed after saline submucosal injection with adequate lifting. This case was considered therapeutic failure. However, there may be cases like

this in which CEMR can be complementary to UEMR and vice versa. Despite the floatage and lifting, this lesion had deep submucosal invasion (SM3). In addition to this described case, there were two more lesions with submucosal invasion (SM2). And in all cases (even those with deep invasion) there was good buoyancy. Although not yet discussed in the literature, it would be expected that invasive lesions will not float; being a rational analogy between the "lifting-sign" and the "floating-sign". However, even the reliability of the "lifting-sign" in predicting invasive malignancy has been questioned. A multicenter study found around 40% of lesions with invasion beyond 1000 μm with a false negative non-"lifting-sign", and the endoscopic evaluation to be more reliable than the "lifting-sign"[18].

The rate of submucosal invasion in our study was 6.2% which is similar to the recent UEMR meta-analysis (5.9%)[14] and slightly smaller to the 8% reported in conventional EMR and/or polypectomy meta-analysis[19].

The procedure time in our study ranged from 4 to 40 minutes, with a mean time of 12 minutes. Similar to the mean time described by Curcio et al.[1] (11.8 minutes). Most of the time was spent on the marking of the lesion rather than on the submerged phase itself (subjective analysis), and unfortunately the time was only recorded in just over half of the procedures (55%).

Safety is an aspect that draws attention with the underwater technique. There is a relatively low incidence of adverse events, and the vast majority of them had a conservative management[1,4-14]. The total incidence of adverse events in our study was 5.4%. There were two immediate bleeding episodes (3.6%), both successfully treated endoscopically with clips. The hemorrhage rate after UEMR in the literature ranged from 0% to 18%, with only a few cases of delayed bleeding described[1]. According to Spadaccini et al.[14] meta-analysis, the during-UEMR procedure bleeding rate was 3.14% and post procedural hemorrhage rate occurred in 2.85%[14]. Also worthy of mention is the bleeding post resection treatment when the intestine is filled with water, as the bleeding point can accurately be identified when using water irrigations[5]. A peculiar aspect with our work is that major bleeds only occurred with the use of AUTOCUT mode. However, without further investigation, it is impossible to draw any conclusion between the electrosurgical setting and the incidence of bleeding. In this study, there was one case of post-polypectomy syndrome. To our knowledge, this is the first case of post-polypectomy syndrome described in the literature. In our study, as in others, there were no cases of perforation. As far as we know, only two cases of perforation post UEMR have been described. One case was in a retroflexion maneuver that may be related to this adverse event[20]. The other case occurred when it was injected into the submucosa before the UEMR (hybrid technique)[16]. The authors of this paper also suggest that stretching of the colonic wall by the submucosal injection is probably to be the cause. Therefore, until further studies are conducted about the relation between retroflexion and hybrid technique with the perforation after underwater resection, we recommend that UEMR should be performed only in forward view and without submucosal injection.

The incidence of recurrence after UEMR in the literature varied between null and 20%, being 8.82% in UEMR systematic review[14]. In our study, the recurrence rate was 6%, comparable to that described by Schenck et al.[4] (7.3%). Unfortunately, a lower-than-expected number of patients had endoscopic surveillance (74.54%), with a significant percentage of patients who died or were too ill to undergo colonoscopy. In addition, endoscopic surveillance in our study was performed with white light, virtual chromoscopy (NBI), conventional (indigo carmine), and biopsy of the scars, which may increase the sensitivity[21].

The number of patients underwent to UEMR in our cohort was surpassed only by Curcio et al.[1], Binmoeller et al.[12], Siau et al.[15] and Yamashina et al.[9]; being the Brazilian study about UEMR with more patients.

In summary, UEMR seems to be safe and effective. Taken together, our results and the data in the literature encourage the dissemination of the method. A natural issue is the comparison with the submucosal injection technique. In a retrospective study, Schenck et al.[4] observed similar safety with both methods (CEMR and UEMR), however, there was superiority in terms of complete resection indexes, and a lower frequency of recurrence with the underwater technique. In a recent prospective randomized study, the en bloc resection rate was higher with UEMR than CEMR, without significant difference with adverse events[9]. More trials with a larger casuistry and with long-term follow-up are needed for more consistent conclusions. We hope that we can finalize our randomized study (NCT03021135) soon to help answer these questions.

Authors' contribution

Data curation: Lenz L, Martins B, Kawaguti FS, Tellian A, Pennachi CMPS, Sorbello M, Gusmon C, Paulo GA, Uemura R, Geiger S, Lima MS, Safatle-Ribeiro A, Baba E, Hashimoto CL, Maluf-Filho F, Ribeiro Jr U. Resources: Martins B. Investigation: Kawaguti FS, Lima MS, Geiger S, Baba E, Hashimoto CL, Maluf-Filho F. Conceptualization: Lenz L, Martins B, Paulo GA, Safatle-Ribeiro A, Hashimoto CL, Maluf-Filho F, Ribeiro Jr U. Formal analysis: Lenz L, Maluf-Filho F. Methodology: Lenz L, Martins B, Paulo GA, Baba E, Hashimoto CL, Maluf-Filho F, Ribeiro Jr U. Visualization: Lenz L, Kawaguti FS, Paulo GA, Lima MS, Safatle-Ribeiro A, Hashimoto CL, Maluf-Filho F. Writing-original draft: Lenz L, Kawaguti FS, Safatle-Ribeiro A, Maluf-Filho F. Writing-review & editing: Lenz L, Martins B, Safatle-Ribeiro A, Maluf-Filho F. Project administration: Lenz L, Martins B, Paulo GA, Maluf-Filho F, Ribeiro Jr U. Supervision: Lenz L, Maluf-Filho F, Ribeiro Jr U. Validation: Safatle-Ribeiro A, Maluf-Filho F.

Orcid

Luciano Lenz: 0000-0002-7945-8158.
Bruno Martins: 0000-0002-0282-0753.
Fabio Shiguehisa Kawaguti: 0000-0002-6709-9979.
Alexandre Tellian: 0000-0002-2279-6623.
Caterina Maria Pia Simoni Pennachi: 0000-0001-6963-8211.
Mauricio Sorbello: 0000-0002-4021-6573.
Carla Gusmon: 0000-0003-3803-3417.
Gustavo Andrade de Paulo: 0000-0002-7926-9373.
Ricardo Uemura: 0000-0002-2970-7136.
Sebastian Geiger: 0000-0001-6626-9131.
Marcelo Simas de Lima: 0000-0002-4601-7276.
Adriana Safatle-Ribeiro: 0000-0001-7686-8859.
Elisa Baba: 0000-0001-7261-9054.
Claudio Lyoiti Hashimoto: 0000-0002-5763-339X.
Fauze Maluf-Filho: 0000-0001-8875-420X.
Ulysses Ribeiro Jr: 0000-0003-1711-7347.

Lenz L, Martins B, Kawaguti FS, Tellian A, Pennachi CMPS, Sorbello M, Gusmon C, Paulo GA, Uemura R, Geiger S, Lima MS, Safatle-Ribeiro A, Baba E, Hashimoto CL, Maluf-Filho F, Ribeiro Jr U. Ressecção da mucosa endoscópica sob imersão d'água para lesões colorretais não pediculadas. Um estudo prospectivo de braço único. Arq Gastroenterol. 2020;57(2):193-7.

RESUMO – **Contexto** – A ressecção endoscópica da mucosa sob imersão d'água (REMS) surgiu como um método revolucionário que permite a ressecção de lesões colorretais sem injeção submucosa. A literatura brasileira sobre essa técnica é escassa. **Objetivo** – A finalidade deste estudo foi avaliar a eficácia e segurança da técnica REMS na remoção de lesões colorretais não pediculadas em dois centros terciários brasileiros. **Métodos** – Este estudo prospectivo foi realizado entre junho de 2016 e maio de 2017. As lesões sem tentativa de ressecção prévia, não pediculadas e sem sinais de invasão submucosa foram ressecadas pela técnica REMS. **Resultados** – Um total de 55 pacientes com 65 lesões foram incluídos. Todas as lesões, exceto uma, foram removidas com sucesso e completamente por REMS (taxa de sucesso de 98,5%). Durante a REMS, foram observados dois casos de sangramento (3,0%). Uma paciente apresentou dor abdominal no dia seguinte à ressecção sem pneumoperitônio. Não houve perfuração ou sangramento tardio. **Conclusão** – Este estudo apoia os dados existentes, indicando taxas aceitáveis de sucesso técnico e baixa incidência de eventos adversos com a REMS. Os resultados deste estudo brasileiro foram consistentes com estudos internacionais prévios.

DESCRITORES – Pólipos intestinais. Neoplasias colorretais. Ressecção endoscópica de mucosa. Imersão. Estudos prospectivos.

REFERENCES

1. Curcio G, Granata A, Ligresti D, Tarantino I, Barresi L, Liotta R, et al. Underwater colorectal EMR : remodeling endoscopic mucosal resection. Gastrointest Endosc [Internet]. 2015;81:1238-42.
2. Conio M, Repici A, Demarquay JF, Blanchi S, Dumas R, Filiberti R. EMR of large sessile colorectal polyps. Gastrointest Endosc. 2004;60:234-41.
3. Nanda KS, Bourke MJ. Endoscopic mucosal resection and complications. Tech Gastrointest Endosc. 2013;15:88-95.
4. Schenck RJ, Jahann DA, Patrie JT, Stelow EB, Cox DG, Uppal DS, et al. Underwater endoscopic mucosal resection is associated with fewer recurrences and earlier curative resections compared to conventional endoscopic mucosal resection for large colorectal polyps. Surg Endosc Other Interv Tech. 2017;31:4174-83.
5. Binmoeller KF, Weilert F, Shah J, Bhat Y, Kane S. "Underwater" EMR without submucosal injection for large sessile colorectal polyps (with video). Gastrointest Endosc. 2012;75:1086-91.
6. Amato A, Radaelli F, Spinzi G. Underwater endoscopic mucosal resection: The third way for en bloc resection of colonic lesions? United Eur Gastroenterol J. 2016;4:595-8.
7. Chaves D, Brito HP, Chaves LT, Rodrigues RA, Sugai BM. Underwater endoscopic mucosal resection of serrated adenomas. Clinics. 2018;73:e339.
8. Wang AY, Flynn MM, Patrie JT, Cox DG, Bleibel W, Mann JA, et al. Underwater endoscopic mucosal resection of colorectal neoplasia is easily learned, efficacious, and safe. Surg Endosc. 2014;1348-54.
9. Yamashina T, Uedo N, Akasaka T, Iwatsubo T, Nakatani Y, Akamatsu T, et al. Comparison of Underwater vs Conventional Endoscopic Mucosal Resection of Intermediate-Size Colorectal Polyps. Gastroenterology. 2019;157:451-461.e2.
10. Uedo N, Nemeth A, Johansson GW, Toth E, Thorlacius H, Thorlacius H. Underwater endoscopic mucosal resection of large colorectal lesions. Endoscopy. 2015;172-4.
11. Binmoeller KF. Underwater endoscopic mucosal resection. J Interv Gastroenterol. 2014;4:113.
12. Binmoeller KF, Hamerski CM, Shah JN, Weilert F, Shah JN, Bhat Y, et al. Attempted underwater en bloc resection for large (2-4 cm) colorectal laterally spreading tumors (with video). Gastrointest Endosc. 2015;112:713-8.
13. Chaves DM, Brito HP, Chaves LT, Safatle-Ribeiro AV, Fava G, de Moura EGH, et al. Underwater endoscopic resection: an alternative for difficult colorectal polyps. VideoGIE. 2016;1:82-4.
14. Spadaccini M, Lamonaca L, Maselli R, Di Leo M, Galtieri PA, Craviotto V, et al. Underwater EMR for colorectal lesions: a systematic review with meta-analysis (with video). Gastrointest Endosc. 2019;89:1109-1116.e4
15. Siau K, Ishaq S, Cadoni S, Kuwai T, Yusuf A, Suzuki N. Feasibility and outcomes of underwater endoscopic mucosal resection for ≥ 10 mm colorectal polyps. Surg Endosc Other Interv Tech [Internet]. 2018;32:2656-63.
16. Kawamura T, Sakai H, Ogawa T, Sakiyama N, Ueda Y, Shirakawa A, et al. Feasibility of Underwater Endoscopic Mucosal Resection for Colorectal Lesions: A Single Center Study in Japan. Gastroenterol Res. 2018;11:274-9.
17. Kim HG, Thosani N, Banerjee S, Chen A, Friedland S. Underwater endoscopic mucosal resection for recurrences after previous piecemeal resection of colorectal polyps (with video). Gastrointest Endosc. 2014;80:1094-102.
18. Kobayashi N, Saito Y, Sano Y, Uragami N, Michita T, Saito D. Determining the treatment strategy for colorectal neoplastic lesions: endoscopic assessment or the non−lifting sign for diagnosing invasion depth? Endoscopy. 2007;39:701-5.
19. Hassan C, Repici A, Sharma P, Correale L, Zullo A, Bretthauer M, et al. Efficacy and safety of endoscopic resection of large colorectal polyps: A systematic review and meta-analysis. Gut. 2016;65:806-20.
20. Ponugoti PL, Rex DK. Perforation during underwater EMR. Gastrointest Endosc. 2016;84:543-4.
21. Desomer L, Tutticci N, Tate DJ, Williams SJ, McLeod D, Bourke MJ. A standardized imaging protocol is accurate in detecting recurrence after EMR. Gastrointest Endosc. 2017;85:518-26.

ORIGINAL ARTICLE

AG-2020-12
doi.org/10.1590/S0004-2803.202000000-38

Outlet obstructed constipation and fecal incontinence: is rehabilitation treatment the way? Myth or reality

Luigi **BRUSCIANO**[1], Claudio **GAMBARDELLA**[1,2], Gianmattia **DEL GENIO**[1], Salvatore **TOLONE**[1], Francesco Saverio **LUCIDO**[1], Gianmattia **TERRACCIANO**[1], Giorgia **GUALTIERI**[1] and Ludovico **DOCIMO**[1]

Received: 3 February 2020
Accepted: 12 February 2020

ABSTRACT – Pelvic floor rehabilitation aims to address perineal functional and anatomic alterations as well as thoraco-abdominal mechanic dysfunctions leading to procto-urologic diseases like constipation, fecal and urinary incontinence, and pelvic pain. They require a multidimensional approach, with a significant impact on patients quality of life. An exhaustive clinical and instrumental protocol to assess defecation disorders should include clinical and instrumental evaluation as well as several clinical/physiatric parameters. All these parameters must be considered in order to recognize and define any potential factor playing a role in the functional aspects of incontinence, constipation and pelvic pain. After such evaluation, having precisely identified any thoraco-abdomino-perineal anatomic and functional alterations, a pelvi-perineal rehabilitation program can be carried out to correct the abovementioned alterations and to obtain clinical improvement. The success of the rehabilitative process is linked to several factors such as a careful evaluation of the patient, aimed to select the most appropriate and specific targeted rehabilitative therapy, the therapist's scrupulous hard work, especially as regards the patient's emotional and psychic state, and finally the patient's compliance in undertaking the therapy itself, especially at home. These factors may deeply influence the overall outcomes of the rehabilitative therapies, ranging from "real" success to illusion "myth".

HEADINGS – Constipation. Intestinal obstruction. Fecal incontinence. Pelvic floor disorders, rehabilitation. Physical therapy modalities.

Keypoints

- Patients affected by defecatory disorders necessitate by a novel multidimensional approach.
- In addition to the well knowledge pelvic floor evaluation (clinical scores and instrumental features) we propose a clinical-physiatric assessment.
- The clinical-physiatric evaluation add a functional evaluation of thorax, abdomen and perineum all considered as three different parts of the same whole.

INTRODUCTION

Pelvic floor dysfunction is a widespread condition caused by injury, alteration and degeneration of pelvic floor support tissues and, as any functional disorder, it is related to either anatomical or functional factors. It is a complex nosographic entity whose correct identification requires a multidimensional approach, with a significant impact on patients daily activity and quality of life. Currently, in order to reduce the possibility of postoperative inadequate results or complications, several surgeons tend to address these patients to pelvic floor rehabilitation, without a careful clinical and instrumental evaluation. Achieving good long-term outcome is an ambitious project, that needs to be well investigated and standardized. It is in fact of paramount importance to accomplish a detailed evaluation of physiatric and instrumental features in order to identify patient's suitableness for pelvi-perineal rehabilitation treatment. The paper aims to exhaustively analyze the functional aspects involved in those physio-pathologic mechanisms that lead to pelvic disorders (e.g. constipation, fecal and urinary incontinence), and to describe the currently available re-educational and rehabilitative tools based on our referral center experience.

Bowel ano-rectal disorders

Constipation and fecal incontinence are very common in developed countries with 12% to 19% of adults being affected. They are the most common defecatory disorders, recognizing functional and anatomical basis. Constipation consists in the difficult defecation of hard stools, that leads to a prolonged single evacuation (over 15 minutes), increased straining and tenesmus. It is either related to an inadequate introduction of dietary elements or to colorectal anatomical or functional disorders[1]. Constipation can in fact be simply related to a bad bowel management as happening for an apparently broken-down car suspected of engine failure, resulting in just lack of fuel instead. Thus, colon needs its fuel that is composed of three elements that are water, fibers and probiotics. An adequate diagnostic process about constipation shouldn't in fact lack of information about the stool feces[2]. On the other hand,

Declared conflict of interest of all authors: none
Disclosure of funding: no funding received
[1] University of Campania "Luigi Vanvitelli", Division of General, Mininvasive and Bariatric Surgery, Naples, Italy. [2] University of Campania "Luigi Vanvitelli", School of Medicine, Department of Cardiothoracic Sciences, Naples, Italy.
Corresponding author: Claudio Gambardella, MD, PhD. E-Mail: claudiog86@hotmail.it

constipation may have functional causes such as compromised coordination between rectum and anus and an altered synergy of thoraco-abdominal muscles (both improvable with rehabilitation treatment)[3-7]. Functional constipation can be defined as "colic" when associated to a slow colonic transit and "rectal", when associated to pelviperineal dyssynergia (outlet dysfunction type). Obviously, rectal constipation can be determined by anatomical defects of the rectum itself, such as rectocele and recto-rectal intussusception. Such anatomical alterations can only be treated by a surgical approach. Pelviperineal rehabilitation is nowadays recognized as a proper treatment approach for constipation, associated with dietary and behavioral modifications when failure of conventional therapies may occur, when the diagnosis of anorectal functional constipation is correct, and the coordination disturbance is studied and clinically severe[8]. Fecal incontinence (patient's impossibility to hold feces or gas), is as well largely associated to functional alterations such as sphincteral muscular deficit, sensory deficit or muscular innervation deficit, all of these features can be amended by adequate pelvic floor rehabilitation. Pelvic floor rehabilitation has a sort of established indication in fecal incontinence, according to literature in fact, pelvic floor rehabilitation may only be certainly useful for active incontinence even though, in passive incontinence, rehabilitation may be used to obtain striated muscle strengthening and a better awareness of the pelvic floor for better symptom management[8]. In our referral centre, we've had discrete results both in active, passive and mixed incontinence when due to functional matters. Certainly, concomitant anatomical alterations like anal sphincteral damage or previous rectal surgery can make rehabilitation programs less effective and should be addressed to surgery.

FUNCTIONAL ASSESSMENT

Clinical-physiatric evaluation

In order to improve pelvic floor dynamics, proctologists should identify causes of pathologic evacuation. A physiological defecation act is not only controlled by rectal and anal synergy, but also by muscular dynamics between thorax, abdomen and perineum, in addition to a correct posture. The ability in realizing correct synergic movements is in fact not always properly developed in general population[9-12]. Literature data is still very poor on this topic: there's lack of a proper set of values that might help objectifying when to indicate pelvic floor rehabilitation and how to quantify results. Thus, in consideration of the difficulty of obtaining shared normal values, every centre still uses its own values and clinical evaluations to deal with this kind of approach. Evaluation of patients reporting pelvic floor dysfunction is now committed to different clinical or instrumental scores, only graduating the presence and severity of the disease as Wexner and Altomare scores[13-16].

We believe, instead, that a proper diagnostic process should combine, in addition to clinical and instrumental values, several clinical/physiatric parameters such as puborectalis muscle function, perineal defense reflex, agonist and antagonist muscle synergies, and last but not least, postural examination (lumbar lordosis) and respiratory function. We are aware that this kind of diagnostic approach is not standardized or objectionable yet, but our beliefs are strongly supported by our large clinical experience. In our protocol all these parameters must be considered in order to recognize and define any functional aspect of incontinence, constipation and pelvic pain[16,17]. We currently study all of these aspects as follows:

Puborectalis function can be evaluated with rectal exploration, but also with anorectal manometry, dynamic defecography and transanal ultrasonography. If the pubo-rectal muscle relaxes, the axis between the rectum and anal canal aligns, and the stool can transit. This explains the importance of pubo-rectal muscle evaluation to define whether relaxation is absent, incomplete or paradoxical.

The pubococcygeal test (PC) is performed by inserting a finger, hooking the anal canal and vagina in order to evaluate muscle tonic and phasic contraction, muscular strength and symmetry of the left and right muscular branches.

Perineal defense reflex is considered as an expression of correct abdomino-perineal dynamics[18-21]. It evaluates the action of the pelvic floor during forced expiration, when the diaphragm generates a high intra-abdominal pressure. The patient is asked to cough, to allow the proctologist to register the contraction of perianal muscles, that cause a physiological increase (positive reflex) or a pathological drop (negative reflex). Pathological drop is associated with urinary, gas incontinence and soiling[18-20]. It is mandatory to also evaluate muscular synergies by anal contraction with the patient in Sims position[22,23]. The recruitment of agonist muscles, such as the gluteus and abductor groups, during anal sphincter contraction can be caused by the patient's incapacity to selectively recruit the correct muscles for the requested order[24]. Vice versa, the identification of antagonist muscles, (abdominals) during the anal sphincter contraction phase represents a conflict between the abdominal and perineal muscles. *Posture* may also affect pelvic floor dissynergies[25,26]. Its examination should be performed by a plumb line, that helps evaluating lumbar lordosis. It impacts on orientation of the sacral promontory, anorectal angle and puborectal tone. All these important functional and anatomical parameters are part of the clinical physiatric Brusciano Rehabilitation Score System[17].

Respiratory dynamic correlation

A physiologic defecation is not only related to a correct action of the pelvic floor, but also requires a synergic function of thoracic and abdominal muscles[5,6]. The rectal filling sensation works as trigger for the defecatory act, then a Valsalva maneuver is physiologically requested; thoracic diaphragm is pushed downward, abdominal muscles are contracted, and the pelvi-perineal floor descend determining a significant increase of the intra-rectal pressure with an effective straining on defecation. Although, if our target is to improve perineal function and ameliorate defecation, it is mandatory to also highlight the contribution of either diaphragm and abdominal muscles to the Valsalva maneuver[6,7]. As by now it is well known, this maneuver is mainly affected by the position of diaphragm during the maximal intraabdominal strength. Indeed, the pression generated inside the abdominal cavity is inversely proportional to the radius of the sphere (Laplace's law). Given the tension of the contracted anterior abdominal wall along with the proper alignment of the spinal column, the other element playing a substantial role in either reducing volume or increasing intraabdominal pressure, is contraction and descent of the diaphragmatic muscles. This movement may appear simple and ordinary, but it is largely affected instead by the type and method of respiratory mechanics. "Costal" breathing achieves a minimal upper/lower movement, while a correct "diaphragmatic" breath allows a wider excursion. In patients with predominant costal breathing, an absent or ineffective diaphragmatic movement can be improved by simple exercises focused on respiratory coordination[5,6].

Instrumental evaluation

Instrumental indexes, especially manometric ones, are nowadays deeply known and fully used to indicate rehabilitation. What we aim to add, is that objective parameters alone do not complete the diagnostic process, if they are not properly inserted in the patient functional evaluation of thorax, abdomen and perineum; all considered as three different parts of the same whole. The clinical-physiatric evaluation we apply in our referral centre can in fact be considered a novel approach in the assessment of the pelvic floor dysfunctional patient. Nevertheless, in order to achieve a full evaluation of the functional or anatomical alterations, instrumental findings are mandatory. The anorectal manometry evaluates the pressures and volumes of the rectum and anal canal, highlighting significant alterations in patients with constipation and incontinence. Incontinence is often characterized by lower basal pressures and lower pressure during voluntary contraction, as reflected by altered rectal sensitivity and recto-anal inhibitory reflex. Rectal compliance is reduced with increased spontaneous relaxations. In constipation, anal pressure profile can either be normal or hypertonic, but associated with altered recto-anal inhibitory reflex and reduced sensibility to defecate, only evocated by higher volumes. This is consistent with the principle that the association of adequate anal canal relaxation and lower residual pressure determines a sufficient gradient for defecation[27-30]. Defecography shows better than any other investigation the rectal morphology by showing the relationship between the anal canal and pubococcygeal level (i.e. rectocele or recto-rectal intussusceptions), and investigating them during defecatory function (e.g. rest, straining and defecation act). An incomplete or absent relaxation of the puborectal muscle, with the subsequent incomplete or absent extension of anorectal angle, is a typical finding of constipation. In incontinent patients the most common feature is the loss of barium particles during coughing. Endoanal and perineal ultrasound is mandatory to exclude presence of sphincteral defects (i.e. lesions, inhomogeneity, outright interruptions) that can cause idiopathic or traumatic incontinence, and moreover it is able to asses puborectal muscle function[31,32].

Rehabilitation treatment

Rehabilitation should start with a patient's re-educational phase. This process aims to improve an altered bodily function; it is not merely cognitive, while it prepares the patient toward an active, rather than a passive, role with a deep participation during the healing process. Even according to Bocchini et al., this phase is as important as the others as it has the aim of improving anorectal physiological functions corticalization through a progressively better awareness of such body areas[2].

The second phase aims to heal functional alterations by different techniques (biofeedback, electrostimulation, physiokinesitherapy and volumetric rehabilitation) in order to address every single alteration. These techniques should be considered as systematic part of a whole process, not single separable steps, and therefore an undetermined and unweighted medical indication of "just do a biofeedback!" should be avoided[33].

Correct rehabilitation is composed of three main steps:

1. Re-educational feature: patients are taught anatomical and physiological functions of the body area which will be treated, in order to best interact during rehabilitation; they have to gain proper acknowledge about anatomical and functional aspects of their perineum in order to correctly govern it.
2. Practical exercise to obtain functional and postural recovery. In case of electrostimulation, anal or vaginal probes perform electrical stimulation of nerves and muscles, allowing an appropriate and precise visualization of patient's muscular activity. Given probes are connected to a monitor, patients can observe their muscular activity simultaneously (biofeedback), learning coordination while eliminating their mistakes. Its reliability to increase the patient's awareness during both contraction and relaxation training is now well assessed[34]. The volumetric rehabilitation method artificially simulates urge or delayed need to defecate, trough graduated enema, modulating rectal sensibility threshold with the aim of normalizing their physiological function. In addition, with physiokinesitherapy the rehabilitator basically uses their hands to rebalance bodily functions, after a careful evaluation of the patient's osteo-muscular state. It is in fact an active technique with the aim of allowing the patient to learn or re-learn correct muscle and functional behaviors forgotten or never learnt, in order to lead to a normal defecation. Assisted and against-resistance exercises are performed to adequately stimulate the perineal muscles and properly involve synergic muscles and those of the anal sphincter. In this phase, the patient is also trained throughout easy exercises on how to gain the correct respiratory dynamics because of the contribution of either diaphragm and abdominal muscles to the Valsalva maneuver, as explained before.
3. Home self-executing of gained movements and consciousness in everyday life, as natural patient's behavior.

In order to reach a successful rehabilitation and maintain a normal bodily function, patients should keep what they have learned about bodily anatomy and rehabilitation exercises, with a complete summarize and correct coordination of the techniques during everyday life.

Rehabilitation therefore begins in the rehabilitative ambulatory but continues at home and is constantly carried out until the patient is healed and thereafter (like in every workout training). Moreover, advantages of rehabilitation program can only be effective if patient actively participates not only physically, but also mentally[35].

CONCLUSION

The overall path of rehabilitation consists in strengthening and harmonizing the different muscles of the pelvic floor, not only with their self but also with the rest of the body. The acts of retention or expulsion (urinating and/or defecating) does not solely depend upon the pelvic floor but it consists in a complex result of simultaneous coordination with the pelvic floor itself, with the chest and abdomen. For an exhaustive assessment of a dysfunctional patient, clinical status, instrumental features, and physiatric patterns, should be evaluated in order to define which patients will best benefit from a pelviperineal rehabilitation program[17]. It should be modulated on patient's emotional and psychic state, and its ability to collaborate in undertaking a proper therapy when back home.

Thus, the mere correction of single alterations found during the physio-clinical study might not be effective in healing every defecatory or urinary disorder and their related symptoms, but surely improves the clinical conditions with positive impact on Wexner and Pescatori score. On the other hand, the improvements of Brusciano Score parameters could not reflect in a clinically relevant improvement of symptoms. Overall outcomes of the

rehabilitative process are linked to several different factors and may deeply change results, ranging from "real" success to illusion "myth". It is clear why surgery should be considered as a standard of care only in case of clinical symptoms related to not modifiable anatomical defects.

This paper aims to spread the concept that pelvi-perineal rehabilitation should be adopted as part of a multi-modal therapy, only after having detected the proper indications, while if it is only suggested in case of failure of previous other treatments, as it usually currently happens, it may achieve poor results and thus remain a false "myth".

Authors' contribution

Brusciano L and Gambardella C contributed to conception, design and drafting of the article; del Genio G, Tolone S, Terracciano G, Gualtieri G and Lucido FS contributed to acquisition and interpretation of data; Docimo L revised it critically and gave final approval of the version to be published.

Orcid

Luigi Brusciano: 0000-0003-4112-1282.
Claudio Gambardella: 0000-0003-2277-2960.
Gianmattia del Genio: 0000-0001-5603-8970.
Salvatore Tolone: 0000-0002-1653-9903.
Francesco Saverio Lucido: 0000-0002-8778-4690.
Gianmattia Terracciano: 0000-0002-3759-1583.
Giorgia Gualtieri: 0000-0002-9591-1856.
Ludovico Docimo: 0000-0001-5587-9452.

Brusciano L, Gambardella C, del Genio G, Tolone S, Lucido FS, Terracciano G, Gualtieri G, Docimo L. Constipação com obstrução à saída e incontinência fecal: o tratamento de reabilitação é o caminho? Mito ou realidade. Arq Gastroenterol. 2020;57(2):198-202.

RESUMO – A reabilitação do assoalho pélvico visa abordar alterações funcionais e anatômicas perineais, bem como disfunções mecânicas torácicas-abdominais que levam a doenças procto-urológicas como prisão de ventre, incontinência fecal e urinária e dor pélvica. Requerem uma abordagem multidimensional, com impacto significativo na qualidade de vida dos pacientes. Um protocolo clínico e instrumental exaustivo para avaliar os transtornos de defecação deve incluir avaliação clínica e instrumental, bem como diversos parâmetros clínicos/fisiátricos. Todos esses parâmetros devem ser considerados para reconhecer e definir qualquer fator potencial desempenhando um papel nos aspectos funcionais da incontinência, prisão de ventre e dor pélvica. Após tal avaliação, tendo identificado com precisão quaisquer alterações anatômicas e funcionais tóraco-abdomino-perineais, um programa de reabilitação pelvi-perineal pode ser realizado para corrigir as alterações acima mencionadas e obter melhora clínica. O sucesso do processo de reabilitação está ligado a diversos fatores, como uma avaliação cuidadosa do paciente, visando selecionar a terapia de reabilitação direcionada mais adequada e específica, além do trabalho árduo e escrupuloso do terapeuta, especialmente no que diz respeito ao estado emocional e psíquico do paciente e, finalmente, a conformidade do paciente em realizar a terapia em si, especialmente em casa. Esses fatores podem influenciar profundamente os resultados globais das terapias de reabilitação, que vão desde o sucesso "real" até o "mito" ilusório.

DESCRITORES – Constipação intestinal. Obstrução intestinal. Incontinência fecal. Distúrbios do assoalho pélvico, reabilitação. Modalidades de fisioterapia.

REFERENCES

1. Brusciano L, Limongelli P, del Genio G, Rossetti G, Sansone S, Healey A, et al. Clinical and instrumental parameters in patients with constipation and incontinence: their potential implications in the functional aspects of these disorders. Int J Colorectal Dis. 2009;24:961-7.
2. Lewis SJ, Heaton KW. Stool form scale as a useful guide to intestinal transit time. Scand J Gastroenterol. 1997;32:920-4.
3. Higgins PD, Johanson JF. Epidemiology of constipation in North America: a systematic review. Am J Gastroenterol. 2004;99:750-9.
4. Pucciani F, Rottoli ML, Bologna A, Cianchi F, Forconi S, Cutellè M, Cortesini C. Pelvic floor dyssynergia and bimodal rehabilitation: results of combined pelviperineal kinesitherapy and biofeedback training. Int J ColorectDis. 1998;13:124-30.
5. Pucciani F, Iozzi L, Masi A, Cianchi F, Cortesini C. Multimodal rehabilitation for faecal incontinence: experience of an Italian centre devoted to faecal disorder rehabilitation. Tech Coloproctol. 2003;7:139-47.
6. Chiarioni G, Whitehead WE, Pezza V, Morelli A, Bassotti G. Biofeedback is superior to laxatives for normal transit constipation due to pelvic floor dyssynergia. Gastroenterology. 2006;130:657-64.
7. Battaglia E, Serra AM, Buonafede G, Dughera L, Chistolini F, Morelli A, et al. Long-term study on the effects of visual biofeedback and muscle training as a therapeutic modality in pelvic floor dyssynergia and slow transit constipation. Dis Colon Rectum. 2004;47:90-5.
8. Bocchini R, Chiarioni G, Corazziari E, Pucciani F, Torresan F, Alduini P, et al. Pelvic floor rehabilitation for defecation disorders. Tech Coloproctol. 2019;23:101-15.
9. Pages IH, Jahr S, Schaufele MK, Conradi E. Comparative analysis of biofeedback and physical therapy for treatment of urinary stress incontinence in women. Am J Phys Rehabil. 2001;80:494-502.
10. Dumoulin C, Seaborne DE, Quirion-DeGirardi C, Sullivan SJ. Pelvic-floor rehabilitation, part 2: pelvic-floor reeducation with interferential currents and exercise in the treatment of genuine stress incontinence in postpartum women-a cohort study. Phys Ther. 1995;75:1075-81.
11. Bourcier AP. Physical therapy for female pelvic floor disorders. Curr Opin Obstet Gynecol. 1994;6:331-5.
12. Galeri S, Sottini C. Physiotherapy of pelvic floor for incontinence. ArchItal Urol Androl. 2001;73:143-6.
13. Altomare DF, Di LM, Giuratrabocchetta S, Giannini I, Falagario M, Zbar AP, Rockwood T. The Three Axial Perineal Evaluation (TAPE) score: a new scoring system for comprehensive evaluation of pelvic floor function. Colorectal Dis. 2014;16:45968.
14. Altomare DF, Di LM, Andriola V, Giuratrabocchetta S, Giannini I, Ferrara C. TriAxial perineal evaluation score: the male version. Colorectal Dis. 2015;17:544-5.
15. Altomare DF, Spazzafumo L, Rinaldi M, Dodi G, Ghiselli R, Piloni V. Set-up and statistical validation of a new scoring system for obstructed defaecation syndrome. Colorectal Dis. 2008;10:84-8.
16. Jorge JM, Wexner SD. Etiology and management of fecal incontinence. Dis Colon Rectum. 1993;36:77-97.
17. Brusciano L, Limongelli P, Del Genio G, Di Stazio C, Rossetti G, Sansone S, et al. Short-term outcomes after rehabilitation treatment in patients selected by a novel rehabilitation score system (Brusciano score) with or without previous stapled transanal rectal resection (STARR) for rectal outlet obstruction. Int J Colorectal Dis. 2013;28:783-93.
18. Rocca Rossetti S. Functional anatomy of pelvic floor. Arch Ital Urol Androl. 2016;88:28-37.

19. Di Benedetto P. La valutazione neuro-fisiatrica perineale. Riabilitazione uro-ginecologica. Edizioni Minerva Medica. 2004;99-103.
20. Brusciano L, Gambardella C, Tolone S, Del Genio G, Terracciano G, Gualtieri G, et al. An imaginary cuboid: chest, abdomen, vertebral column and perineum, different parts of the same whole in the harmonic functioning of the pelvic floor. Tech Coloproctol. 2019;23:603-5. doi: 10.1007/s10151-019-01996-x.
21. Hay-Smith EJ, Dumoulin C. Pelvic floor muscle training versus no treatment, or inactive control treatments, for urinary incontinence in women. Cochrane Database Syst Rev. 2006;1:CD005654.
22. Araujo CC, Coelho SSA, Martinho N, Tanaka M, Jales RM, Juliato CRT. Clinical and ultrasonographic evaluation of the pelvic floor in primiparous women: a cross-sectional study. Int Urogynecol J. 2018;29:1543-9.
23. Herbison P, Plevnik S, Mantle J. Weighted vaginal cones for urinary incontinence. Cochrane Database Syst Rev, 2002.1:CD002114
24. Brusciano L, Limongelli P, del Genio G, Sansone S, Rossetti G, Maffettone V, et al. Useful parameters helping proctologists to identify patients with defaecatory disorders that may be treated with pelvic floor rehabilitation. Tech Coloproctol. 2007;11:45-50.
25. De Troyer A. Mechanical role of the abdominal muscles in relation to posture. Respir Physiol. 1983;53:341-53.
26. Kera T, Maruyama H. The effect of posture on respiratory activity of the abdominal muscles. J Physiol Anthropol Appl Human Sci. 2005;24:259-65.
27. Whitehead WE, Orr WE, Engel BT, Schuster MM. External anal sphincter response to rectal distension: learned response or reflex. Psychophysiology.1982;19:57-62.
28. Caetano AC, Dias S, Santa-Cruz A, Rolanda C. Renzi score for obstructed defecation syndrome - validation of the portuguese version according to the cosmin checklist. Arq Gastroenterol. 2018;55:55-60.
29. Murad-Regadas SM, Regadas FS, Rodrigues LV, Fernandes GO, Buchen G, Kenmoti VT. Management of patients with rectocele, multiple pelvic floor dysfunctions and obstructed defecation syndrome. Arq Gastroenterol. 2012;49:135-42.
30. Teng M, Kervinio F, Moutounaïck M. Review of pelvic and perineal neuromuscular fatigue: Evaluation and impact on therapeutic strategies. Ann Phys Rehabil Med. 2018;61:345-51.
31. Brusciano L, Limongelli P, Pescatori M, Napolitano V, Gagliardi G, Maffettone V, et al. Ultrasonographic patterns in patients with obstructed defaecation. Int J Colorectal Dis. 2007;22:969-97.
32. Kannan P, Winser S, Fung B, Cheing G. Effectiveness of Pelvic Floor Muscle Training Alone and in Combination with Biofeedback, Electrical Stimulation, or Both Compared to Control for Urinary Incontinence in Men Following Prostatectomy: Systematic Review and Meta-Analysis. Phys Ther. 2018;98:932-45.
33. Gambardella C, Brusciano L, Del Genio G, Tolone S, Terracciano G, Gualtieri G. Predictive parameters to identify incontinent patients amenable for rehabilitation treatment: the muscular synergies evaluation. Arq Gastroenterol. 2019;56:452-3.
34. Rao SS, Benninga MA, Bharucha AE, Chiarioni G, Di LC, Whitehead WE. ANMS-ESNM position paper and consensus guidelines on biofeedback therapy for anorectal disorders. Neurogastroenterol Motil. 2015;27:594-609.
35. Del Genio A, Brusciano L, Sansone S. Riabilitazione del Pavimento Pelvico: in colloquio con i pazienti. Naples: Idelson Gnocchi; 2009.

ORIGINAL ARTICLE

AG-2020-21
doi.org/10.1590/S0004-2803.202000000-39

Insulin and insulin receptor gene polymorphisms and susceptibility to nonalcoholic fatty liver disease

Hossein **NOBAKHT**[1], Touraj **MAHMOUDI**[2], Mohammad **SABZIKARIAN**[3], Seidamir Pasha **TABAEIAN**[3], Gholamreza **REZAMAND**[3], Asadollah **ASADI**[4], Hamid **FARAHANI**[5], Reza **DABIRI**[1], Fariborz **MANSOUR-GHANAEI**[6], Iradj **MALEKI**[7] and Mohammad Reza **ZALI**[2]

Received: 18 February 2020
Accepted: 23 March 2020

ABSTRACT – **Background** – Nonalcoholic fatty liver disease (NAFLD) is an increasing global health concern defined by excessive hepatic fat content in the absence of excessive alcohol consumption. **Objective** – Given the pivotal role of insulin resistance in NAFLD, we hypothesized that insulin (INS) and insulin receptor (INSR) gene polymorphisms may be associated with NAFLD risk. **Methods** – A total of 312 subjects, including 153 cases with biopsy-proven NAFLD and 159 controls were enrolled in this case-control study. Four polymorphisms in INS (rs3842752, rs689) and INSR (rs1052371, rs1799817) genes were genotyped using PCR-RFLP method. **Results** – The cases with NAFLD were older and had higher BMI, systolic blood pressure, diastolic blood pressure, as well as higher serum levels of aspartate aminotransferase, alanine aminotransferase, and gamma glutamyl transferase than the controls (P<0.001). The "TT" genotype of INSR rs1799817 compared with "CC" genotype occurred more frequently in the controls than the cases with NAFLD and the difference remained significant after adjustment for confounding factors (P=0.018; OR=0.10, 95%CI=0.02–0.76). However, no significant difference was found for INS rs3842752, INS rs689, and INSR rs1052371 gene polymorphisms between the cases with NAFLD and the controls either before or after adjustment for the confounders. **Conclusion** – These findings corroborate the hypothesis that genetic polymorphisms related to insulin resistance play a role in NAFLD susceptibility. Specifically, the INSR rs1799817 "TT" genotype had a protective effect for NAFLD. However, our results remain to be validated in other studies.

HEADINGS – Non-alcoholic fatty liver disease. Insulin resistance. Insulin receptor. Genetic polymorphism.

INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) – the most prevalent chronic liver disorder – is an increasing and serious worldwide health concern. It is considered the hepatic expression of metabolic syndrome and defined by excessive hepatic fat content in the absence of excessive alcohol consumption. NAFLD encompasses a broad range of histological changes varying from simple steatosis to non-alcoholic steatohepatitis (NASH) with potential for progression to cirrhosis and hepatocellular carcinoma. Owing to the very high global prevalence of NAFLD, twenty-five percent, it is of paramount importance to understand its pathogenesis[1].

Notwithstanding efforts, the etiology of NAFLD and the reasons for its progression to NASH has not been fully comprehended yet. Nevertheless, it is well established that NAFLD is strongly connected with metabolic disorders such as abnormal glucose tolerance[2], insulin resistance (IR)[3,4], type 2 diabetes (T2D)[5], and obesity[6]. So, IR is one of the underlying causes of NAFLD. The severity of histological progression of NAFLD is closely related to insulin sensitivity independent of body mass index (BMI)[7], as well as NASH patients compared with the patients with simple fatty liver have more severe IR[8]. Additionally, NAFLD patients with IR in comparison to those without IR show much higher rates of elevated liver enzymes of aspartate aminotransferase and alanine aminotransferase[9]. Furthermore, NAFLD patients have a higher circulating level of insulin than controls[10]. And finally, significant associations between insulin (INS) and insulin receptor (INSR) gene polymorphisms and circulating insulin levels[11,12], IR[13,14], BMI[15] and risk of T2D[16,17] have been reported.

Therefore, these observations led us to investigate whether insulin resistance-related genes (INS and INSR) were associated with NAFLD risk in Iranian population.

Declared conflict of interest of all authors: none
Disclosure of funding: This work was supported by grants from Iran National Science Foundation (INSF) [grant number 90005942] and Gastroenterology and Liver Diseases Research Center, Shahid Beheshti University of Medical Sciences [grant number 1422].
Researche performed at: Research Institute for Gastroenterology and Liver Diseases, Shahid Beheshti University of Medical Sciences.
[1] Semnan University of Medical Sciences, Internal Medicine Department, Semnan, Iran. [2] Shahid Beheshti University of Medical Sciences, Research Institute for Gastroenterology and Liver Diseases, Gastroenterology and Liver Diseases Research Center, Tehran, Iran. [3] Iran University of Medical Sciences, Colorectal Research Center, Tehran, Iran. [4] University of Mohaghegh Ardabili, Faculty of Science, Department of Biology, Ardabil, Iran. [5] Qom University of Medical Sciences, School of Medicine, Department of Physiology and Pharmacology, Qom, Iran. [6] Guilan University of Medical Sciences, Gastrointestinal and Liver Diseases Research Center (GLDRC), Division of Gastroenterology and Hepatology, Rasht, Iran. [7] Mazandaran University of Medical Sciences, Gut and Liver Research Center, Sari, Iran.
Corresponding author: Touraj Mahmoudi. E-mail: mahmouditouraj@gmail.com

METHODS

Participants

The study population consisted of 159 controls (age range, 33–82 years) and 153 cases with biopsy-proven NAFLD (age range, 32–88 years). This hospital based case-control study was a multicenter research and the centers are as follows: (1) Research Institute for Gastroenterology and Liver Diseases, Shahid Beheshti University of Medical Sciences (2) Gastrointestinal and Liver Diseases Research Center, Guilan University of Medical Sciences (3) Internal Medicine Department, Semnan University of Medical Sciences (4) Colorectal Research Center, Iran University of Medical Sciences (5) Faculty of Science, University of Mohaghegh Ardabili (6) School of Medicine, Qom University of Medical Sciences (7) Gut and Liver Research Center, Mazandaran University of Medical Sciences. All the participants were Iranian and genetically unrelated. They were informed about the aims of the study and their demographic, anthropometric, and clinical information was collected by self-administered questionnaires and before diagnosis of NAFLD. NAFLD diagnosis was established in accordance with the following criteria: (1) ultrasonographic evidence of fatty liver and high serum levels of liver enzymes (ALT, AST, GGT) (2) alcohol consumption <20 g/day in men and <10 g/day in women (3) excluding patients with other causes of liver disease including viral hepatitis, Wilson's disease, alpha-1 antitrypsin deficiency, and use of drugs known to induce steatosis (4) histologic confirmation of NAFLD by an experienced pathologist who was unaware of the patients' clinical and biochemical data and scored biopsies using the Brunt's criteria. Steatosis and necroinflammation were graded from 0 to 3 and fibrosis was staged from 0 to 4[18]. The controls had no liver steatosis (examined by abdominal ultrasonography), neither elevated liver enzymes and viral hepatitis infection (examined by blood test). None of them were alcoholics, drank regularly nor were on regular medications. The controls subjects were recruited from the institute staff and medical students. The Ethical Committee of the Institute reviewed and approved this study which was conducted according to the principles of the Helsinki Declaration. BMI of each subject was calculated by the standard formula: weight kg/height squared (m^2).

Genotype analysis

Five milliliters of peripheral blood samples from each of the 312 subjects were collected in tubes containing ethylene diaminetetraacetic acid (EDTA) as an anticoagulant and store at 4ºC. In this study, genomic DNA was purified from peripheral blood leucocytes using standard methods. Using PCR-RFLP method all the four studied polymorphisms (INS rs3842752, INS rs689, INSR rs1052371, and INSR rs1799817) were genotyped. Our criteria for selecting these SNPs were their position in the gene (exon, promoter or regulatory regions), use in previous genetic studies, and relatively high minor allele frequency (MAF). Moreover, laboratory personnel who carried out the genotyping were blinded to case or control status. TABLE 1 indicates the details of the PCR and RFLP conditions. The PCR products were digested with the appropriate restriction enzymes (Fermentas, Leon-Rot, Germany) and the digested products were run on 2.5% to 3.5% agarose gels and then stained with ethidium bromide for visualization under UV light. Genotyping of the subjects were denoted on the basis of the digestion patterns and the presence or absence of the respective restriction enzymes sites. To check for genotyping error rate, we repeated the genotyping analysis of around 20% of the samples that were selected randomly.

Statistical methods

Chi-square (χ^2) test or t-test were used to compare differences in demographic, anthropometric or clinical parameters between the cases with NAFLD and controls. We also calculated differences in the allele frequencies of polymorphisms between the different groups using χ^2 test. To examine the distribution of the genotype frequencies logistic regression analysis was used. Logistic regression was also computed for adjusting confounding factors such as age and BMI. For all the alleles and genotypes, the odds ratios (OR) which present the measure of associations were given with the respective 95% confidence intervals (95% CI). Statistical analyses were performed with SPSS software for Windows, version 25.0 (SPSS Inc. Chicago, IL, USA). In all statistical tests, a $P<0.05$ was considered to indicate a statistically significant difference.

TABLE 1. Insulin (INS) and insulin receptor (INSR) gene SNPs.

Gene	SNP ID (base change)	Primer sequence (forward and reverse)	Annealing temperature	PCR product size (bp)	Restriction enzyme	RFLP products size (bp)
INS	rs3842752 (C/T)	5'-TGTGGAACAATGCTGTACC-3'	57 ºC	410	PstI	C: 410
		5'-GCTACTGAACAAGAAGTCAC-3'				T: 336+74
INS	rs689 (T/A)	5'-TCCAGGACAGGCTGCATCAG-3'	58 ºC	441	Alw26I	A: 441
		5'-AGCAATGGGCGGTTGGCTCA-3'				T: 230+211
INSR	rs1052371 (T/C)	5'-CTAGTCAAGGTCCAGAACC-3'	57 ºC	224	LweI	T: 224
		5'-AGGCACACAAAGGGACGAG-3'				C: 154+70
INSR	rs1799817 (T/C)	5'-CCAAGGATGCTGTGTAGATAAG-3'	60 ºC	317	Eco72I	T: 317
		5'-TCAGGAAAGCCAGCCCATGTC-3'				C: 274+43

RESULTS

TABLE 2 presents demographic, anthropometric, clinical, and biochemical characteristics of the cases with NAFLD and the controls. The cases were older (P<0.001), more likely to be overweight/obese (P<0.001), males (P<0.001), and smokers (P=0.015) than the controls. Moreover, systolic blood pressure (SBP), diastolic blood pressure (DBP), as well as circulating levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), and gamma glutamyl transferase (GGT) were higher in the cases with NAFLD compared with the controls (P<0.001).

The distribution of genotypes and alleles of INS rs3842752, INS rs689, INSR rs1052371, and INSR rs1799817 gene polymorphisms in cases with NAFLD and controls are provided in TABLE 3. The carriers of the INSR rs1799817 "TT" genotype compared with the carriers of the "CC" genotype were associated with a decreased risk for NAFLD, and the difference remained significant even after adjustment for confounding factors including age, BMI, sex, smoking status, SBP, and DBP (P=0.018; OR=0.10, 95%CI =0.02–0.76). In other words, the INSR rs1799817 "TT" genotype had a 90% decreased risk for NAFLD. Nevertheless, as shown in TABLE 3, no statistically significant difference in genotype or allele frequencies between the two groups of cases and controls was found for INS rs3842752, INS rs689, and INSR rs1052371 gene polymorphisms either before or after adjustment for confounding factors including age, BMI, sex, smoking status, SBP, and DBP.

TABLE 2. Selected variables of the study participants by cases and controls*.

Variables	Controls (n=159)	Cases with nonalcoholic fatty liver disease (n=153)	*P*-value
Age (years)	29.5(7.4)	38.3(9.2)	<0.001
BMI(kg/m^2)	23.7(3.1)	29.2(5.3)	<0.001
Gender			
Men	83(52.2)	112(73.2)	
Women	76(47.8)	41(26.8)	<0.001
Smoking status			
Never smoker	145(91.2)	114(74.5)	
Former smoker	9(5.7)	20(13.1)	
Current smoker	5(3.1)	19(12.4)	0.015
SBP (mmHg)	114.3(13.5)	123.7(15.2)	<0.001
DBP (mmHg)	69.8(8.4)	74.7(9.6)	<0.001
AST (IU/L)	19.8(7.4)	39.1(17.9)	<0.001
ALT (IU/L)	19.6(10.5)	71.9(40.6)	<0.001
GGT (IU/L)	18.7(8.8)	58.0(31.1)	<0.001
Steatosis			
Grade 0		–	
Grade 1		40(26.1)	
Grade 2		82(53.6)	
Grade 3		31(20.3)	
Necroinflammation			
Grade 0		47(30.7)	
Grade 1		59(38.6)	
Grade 2		45(29.4)	
Grade 3		2(1.3)	
Fibrosis			
Stage 0		90(58.8)	
Stage 1		56(36.6)	
Stage 2		7(4.6)	
Stage 3		–	
Stage 4		–	

* Variables presented as mean (SD) or number (%); BMI: Body mass index, SBP: systolic blood pressure, DBP: diastolic blood pressure, AST: aspartate aminotransferase, ALT: alanine aminotransferase, GGT: gamma glutamyl transferase.

TABLE 3. Distribution of insulin (INS) and insulin receptor (INSR) gene polymorphisms in cases with nonalcoholic fatty liver disease (NAFLD) and in controls*.

Gene (variant)	Controls (n=159)	Cases (n=153)	OR (95% CI) *P*-value**
INS (rs3842752)			
Genotype-wise comparison			
CC	124 (78.0)	107 (69.9)	1.0 (reference)
CT	21 (13.2)	34 (22.2)	1.84 (0.41–8.33) 0.427
TT	14 (8.8)	12 (7.9)	0.35 (0.04–3.22) 0.353
CT and TT	35 (22.0)	46 (30.1)	1.07 (0.31–3.72) 0.910
TT versus others	14 (8.8)	12 (7.9)	0.32 (0.04–2.94) 0.315
Allele-wise comparison			
C	269 (84.6)	248 (81.1)	1.0 (reference)
T	49 (15.4)	58 (18.9)	1.28 (0.68–2.41) 0.449
INS (rs689)			
Genotype-wise comparison			
AA	113 (71.1)	104 (68.0)	1.0 (reference)
AT	37 (23.2)	44 (28.7)	1.85 (0.61–7.22) 0.793
TT	9 (5.7)	5 (3.3)	0.68 (0.32–7.02) 0.513
AT and TT	46 (28.9)	49 (32.0)	1.75 (0.88–5.43) 0.311
TT versus others	9 (5.7)	5 (3.3)	0.59 (0.06–-3.76) 0.422
Allele-wise comparison			
A	263 (82.7)	252 (82.4)	1.0 (reference)
T	55 (17.3)	54 (17.6)	1.08 (0.91–1.88) 0.877
INSR (rs1052371)			
Genotype-wise comparison			
TT	110 (69.2)	94 (61.4)	1.0 (reference)
TC	41 (25.8)	53 (34.6)	0.42 (0.05–3.84) 0.443
CC	8 (5.0)	6 (4.0)	1.02 (0.30–3.43) 0.979
TC and CC	49 (30.8)	59 (38.6)	0.86 (0.28–2.68) 0.797
CC versus others	8 (5.0)	6 (4.0)	0.42 (0.05–3.66) 0.431
Allele-wise comparison			
T	261 (82.1)	241 (78.8)	1.0 (reference)
C	57 (17.9)	65 (21.2)	1.23 (0.69–2.18) 0.484
INSR (rs1799817)			
Genotype-wise comparison			
CC	107 (67.3)	105 (68.6)	1.0 (reference)
CT	28 (17.6)	35 (22.9)	0.42 (0.21–1.52) 0.203
TT	24 (15.1)	13 (8.5)	0.10 (0.02–0.76) 0.018
CT and TT	52 (32.7)	48 (31.4)	0.84 (0.35–1.83) 0.417
TT versus others	24 (15.1)	13 (8.5)	0.36 (0.13–1.29) 0.167
Allele-wise comparison			
C	242 (76.1)	245 (80.1)	1.0 (reference)
T	76 (23.9)	61 (19.9)	0.89 (0.64–1.41) 0.520

* Variables presented as number (%). ** Adjusted for age, body mass index (BMI), sex, smoking status, systolic blood pressure (SBP), and diastolic blood pressure (DBP) in genotype--wise comparisons.

DISCUSSION

This case-control study was conducted to explore whether INS and INSR gene polymorphisms were associated with NAFLD risk. The "TT" genotype of INSR rs1799817 compared with "CC" genotype occurred more frequently in controls than cases with NAFLD and consequently "TT" genotype had a protective effect for NAFLD. Furthermore, this difference remained significant after adjustment for confounding factors including age, BMI, sex, smoking status, SBP, and DBP. Nevertheless, no significant difference was found for INSR rs1052371, INS rs3842752, and INS rs689 gene polymorphisms in either genotype or allele frequencies between the cases with NAFLD and the controls.

The underlying mechanisms of the pathogenesis of NAFLD still remain unclear, however, IR plays a pivotal role in the development and progression of NAFLD. IR expedites the release of free fatty acid from adipose tissue and its influx into liver[3,4,19]. Previous epidemiological reports have also revealed that HOMA-IR index is an independent predictor of the severity of liver fibrosis and the risk of disease progression increases in the patients with IR. It appears that insulin secretion increases in NAFLD patients to compensate for reduced insulin sensitivity to maintain glucose homeostasis in these patients[20,21]. NAFLD has a significant genetic basis and its association with gene variants has been investigated over the past two decades. As insulin signaling pathway genes play crucial roles in glucose homeostasis, it is not surprising that they are potential candidate genes for metabolic disorders such as NAFLD and their dysregulation may lead to NAFLD[22].

The INSR gene, containing 22 exons, is located on short arm of chromosome 19 and encodes INSR. INSR mediates the pleiotropic biological actions of insulin through its potential ability for modulation of the expression of target genes. Therefore, any defects in INSR gene might impair the biological response to insulin and lead to IR. Previous studies demonstrated that liver-specific INSR knockout mice suffer from serious insulin resistance and glucose intolerance[23]. And INSR gene mutations were detected in many patients with insulin resistance[24]. Furthermore, INSR gene polymorphisms are associated with plasma insulin concentration[12], IR[13,14], BMI[15] and risk of T2D[16]. In the present study, the associations between INSR rs1052371 and INSR rs1799817 polymorphisms and NAFLD susceptibility were investigated. No significant difference was observed for rs1052371 variant – located in the 3' untranslated region (3'UTR) of the INSR gene – between the cases with NAFLD and the controls. The 3'UTR region plays a key role in regulating gene expression and its mutations have been linked to some diseases including different cancers[25]. Furthermore, the SNPs in UTRs of the INSR gene are associated with insulin resistance[26]. Another polymorphism studied here, rs1799817 located in exon 17 of the INSR gene, was associated with NAFLD risk; the "TT" genotype had a protective effect for NAFLD. The role of exon 17 in the function of INSR gene and insulin signal transduction is vital due to the fact that it encodes the tyrosine kinase domain of INSR protein[27]. Mutations in the tyrosine kinase domain (exon 17–21) of INSR gene cause severe hyperinsulinemia and insulin resistance[28]. Nevertheless, the molecular mechanism through which rs1799817 variant may influence the function of INSR gene is still speculative and unknown. Rs1799817 does not change the amino acid sequence of INSR protein (His1085His), although growing evidence indicates the likely effect of this type of SNPs in altering protein function[29]. The other possible way is the rs1799817 effect on INSR mRNA level through the control of mRNA splicing or mRNA stability. One hypothesis is that the rs1799817 "C" allele gives rise to a defect in the function of INSR protein and, in turn, impairs the biological response to insulin and leads to insulin resistance and finally NAFLD. This theory is biologically plausible and in accordance with it, the "T" allele of INSR rs1799817 polymorphism has a protective effect for T2D[16]. More interestingly, recent evidence has also indicated that the "CC" genotype of rs1799817 significantly increases IR[14]. Additionally, the frequency of the "T" allele was higher in the controls compared with the insulin-resistant subjects[30] and the "T" allele was more frequent in subjects with normal glucose tolerance than cases with type 2 diabetics, emphasizing the protective effect of "T" allele towards insulin resistance[31]. These findings are in concordance with the above hypothesis and our finding. The other possible hypothesis linking INSR rs1799817 variant with NAFLD risk is through linkage disequilibrium. Rs1799817 may not be a functional polymorphism. Instead it might be in complete or partial linkage disequilibrium with an unidentified functional polymorphism of INSR gene. In support of our hypothesis, it has also been demonstrated that the decrease of hepatic CEACAM1 – a transmembrane glycoprotein that undergoes phosphorylation by the insulin receptor tyrosine kinase and promotes the clearance of insulin from the blood largely in liver – causes insulin resistance, hyperinsulinemia, and hepatosteatosis and its overexpression curtails these metabolic abnormalities associated with NAFLD[32]. And finally, gene polymorphisms that impair INSR signaling favor insulin resistance, obesity, and fibrosis development in NAFLD. The ectoenzyme nucleotide pyrophosphate phosphodiesterase 1 (ENPP1) which interacts directly with INSR inhibits insulin signaling and when overexpressed causes insulin resistance. The 121Gln allele of ENPP1 Lys121Gln polymorphism is a gain-of-function allele causing stronger interaction with INSR and inhibition of its kinase activity[22,33].

The other gene studied here, INS, is also involved in maintaining glucose homeostasis. No significant association was detected between the INS rs3842752 variant – located in 3'UTR – and the INS rs689 polymorphism – located in promoter – and NAFLD susceptibility. Alterations in 3'UTR or promoter sequence may directly affect the function of protein. Alternatively, these variations per se might not be functional, instead they can be associated with epigenetic modifications that have functional effects on gene expression[34]. Previous studies have reported elevated insulin concentrations in NAFLD patients than controls[10] as well as significant associations between circulating insulin level and INS gene polymorphisms[11]. Notwithstanding the biological plausibility, INS may not be a predisposing gene for NAFLD. Of course, in order to conclude that the gene does not play a role in the development and progression of NAFLD, other INS gene polymorphisms should be examined in other studies.

The present case-control study was well designed and we conducted multicenter collaborative research. We also used liver biopsy as the gold standard method for confirming the diagnosis of NAFLD. However, when interpreting our results, some potential limitations should be considered. One limitation was the modest sample size that precluded doing detailed analyses. Another limitation was our lack of information on serum levels of insulin as well as HOMA-IR index. The other limitation was a potential information bias from the case-control study design.

CONCLUSION

In summary, our findings reinforce the hypothesis that genetic polymorphisms related to insulin signaling pathway might play a role in NAFLD susceptibility. And interestingly, this observation is relevant from a theoretical viewpoint. Nonetheless, our results remain to be validated in additional investigations.

ACKNOWLEDGEMENTS

The authors thank all patients and healthy blood donors for providing blood samples.

Authors' contribution

Nobakht H: performing the experiments; analysis and interpretation of data; coordination responsibility; drafting of manuscript. Mahmoudi T: study conception and design; supervising the project; analysis and interpretation of data; drafting of manuscript. Sabzikarian M: acquisition of data; performing statistical analyses; drafting of manuscript. Tabaeian SP, Rezamand G, Asadi A, Farahani H, Dabiri R: acquisition of data; survey execution; drafting of manuscript. Mansour-Ghanaei F, Maleki I: acquisition of data; drafting of manuscript. Zali MR: acquisition of data; acquisition of the financial support; drafting of manuscript.

Orcid

Hossein Nobakht: 0000-0001-9386-2280.
Touraj Mahmoudi: 0000-0002-3220-6252.
Mohammad Sabzikarian: 0000-0001-7728-5444.
Seidamir Pasha Tabaeian: 0000-0001-5260-5667.
Gholamreza Rezamand: 0000-0002-4305-2420.
Asadollah Asadi: 0000-0003-3314-2948.
Hamid Farahani: 0000-0002-1262-1854.
Reza Dabiri: 0000-0003-4506-9901.
Fariborz Mansour-Ghanaei: 0000-0002-6264-0025.
Iradj Maleki: 0000-0003-2395-8118.
Mohammad Reza Zali: 0000-0002-9027-4560.

Nobakht H, Mahmoudi T, Sabzikarian M, Tabaeian SP, Rezamand G, Asadi A, Farahani H, Dabiri R, Mansour-Ghanaei F, Maleki I, Zali MR. Insulina e polimorfismos do gene do receptor de insulina e a suscetibilidade à doença hepática gordurosa não alcoólica. Arq Gastroenterol. 2020;57(2):203-8.

RESUMO – **Contexto** – A doença hepática gordurosa não alcoólica (NAFLD) é uma preocupação global crescente da saúde definida pelo excesso de teor de gordura hepática na ausência de consumo excessivo de álcool. **Objetivo** – Dado o papel crucial da resistência à insulina no NAFLD, criou-se a hipótese de que os polimorfismos genéticos da insulina (INS) e do receptor de insulina (INSR) podem estar associados ao risco de NAFLD. **Métodos** – Um total de 312 indivíduos, incluindo 153 casos com NAFLD comprovado por biópsia e 159 controles foram inscritos neste estudo de caso-controle. Quatro polimorfismos em genes INS (rs3842752, rs689) e INSR (rs1052371, rs1799817) foram genotipados utilizando o método PCR-RFLP. **Resultados** – Os casos com NAFLD foram mais idosos e apresentaram maior IMC, pressão arterial sistólica, pressão arterial diastólica, bem como níveis séricos mais elevados de aspartato aminotransferase, de alanina aminotransferase e de gama glutamil transpeptidase do que os controles (*P*<0,001). O genótipo "TT" de INSR rs1799817 em comparação com o genótipo "CC" ocorreu com mais frequência nos controles do que os casos com NAFLD e a diferença permaneceu significativa após ajuste para fatores de confusão (*P*=0,018; OR=0,10, IC95%=0,02–0,76). No entanto, não foi encontrada diferença significativa para INS rs3842752, INS rs689 e INSR rs1052371 polimorfismos genéticos entre os casos com NAFLD e os controles antes ou depois do ajuste para os fatores de confusão. **Conclusão** – Esses achados corroboram a hipótese de que os polimorfismos genéticos relacionados à resistência à insulina desempenham um papel na suscetibilidade do NAFLD. Especificamente, o genótipo INSR rs1799817 "TT" teve um efeito protetor para o NAFLD. No entanto, nossos resultados necessitam ser validados em outros estudos.

DESCRITORES – Hepatopatia gordurosa não alcoólica. Resistência à insulina. Receptor de insulina. Polimorfismo genético.

REFERENCES

1. Araújo AR, Rosso N, Bedogni G, Tiribelli C, Bellentani S. Global epidemiology of non-alcoholic fatty liver disease/non-alcoholic steatohepatitis: What we need in the future. Liver Int. 2018;38:47-51.
2. Haukeland JW, Konopski Z, Linnestad P, Azimy S, Marit Løberg E, Haaland T, et al. Abnormal glucose tolerance is a predictor of steatohepatitis and fibrosis in patients with non-alcoholic fatty liver disease. Scand J Gastroenterol. 2005;40:1469-77.
3. Eguchi Y, Eguchi T, Mizuta T, Ide Y, Yasutake T, Iwakiri R, et al. Visceral fat accumulation and insulin resistance are important factors in nonalcoholic fatty liver disease. J Gastroenterol. 2006;41:462-9.
4. Brunt EM, Kleiner DE, Wilson LA, Unalp A, Behling CE, Lavine JE, et al. NASH Clinical Research Network A list of members of the Nonalcoholic Steatohepatitis Clinical Research Network can be found in the Appendix. Portal chronic inflammation in nonalcoholic fatty liver disease (NAFLD): a histologic marker of advanced NAFLD-Clinicopathologic correlations from the nonalcoholic steatohepatitis clinical research network. Hepatology. 2009;49:809-20.
5. Bellentani S, Scaglioni F, Marino M, Bedogni G. Epidemiology of non-alcoholic fatty liver disease. Dig Dis. 2010;28:155-61.
6. Dietrich P, and Hellerbrand. Non-alcoholic fatty liver disease, obesity and the metabolic syndrome. Best practice and research. Best Pract Res Clin Gastroenterol. 2014;28:637-53.
7. Ohmi S, Ono M, Takata H, Hirano S, Funakoshi S, Nishi Y, et al. Analysis of factors influencing glucose tolerance in Japanese patients with non-alcoholic fatty liver disease. Diabetol Metab Syndr. 2017;9:65.
8. Gholam PM, Flancbaum L, Machan JT, Charney DA, Kotler DP. Nonalcoholic fatty liver disease in severely obese subjects. Am J Gastroenterol. 2007;102:399-408.
9. Li M, Zhang S, Wu Y, Ye J, Cao X, Liu J, et al. Prevalence of insulin resistance in subjects with nonalcoholic fatty liver disease and its predictors in a Chinese population. Dig Dis Sci. 2015;60:2170-6.
10. Siddiqui MS, Fuchs M, Idowu MO, Luketic VA, Boyett S, Sargeant C, et al. Severity of nonalcoholic fatty liver disease and progression to cirrhosis associate with atherogenic lipoprotein profile. Clin Gastroenterol Hepatol. 2015;13:1000-8.
11. Le Stunff C, Fallin D, Schork NJ, Bougnères P. The insulin gene VNTR is associated with fasting insulin levels and development of juvenile obesity. Nat Genet. 2000;26:444-6.
12. Andraweera PH, Gatford KL, Dekker GA, Leemaqz S, Russell D, Thompson SD, et al. Insulin family polymorphisms in pregnancies complicated by small for gestational age infants. Mol Hum Reprod. 2015;21:745-52.
13. Wang L, Mi J, Wu JX, Zhao XY, Cheng H, Ding XY, et al. Study on the relationship between polymorphism of insulin-receptor gene EXON2-2257 and insulin resistance in Chinese people. Zhonghua Liu Xing Bing Xue Za Zhi. 2004;25:49-53.

14. Gangopadhyay S, Agrawal N, Batra A, Kabi BC, Gupta A. Single nucleotide polymorphism on exon 17 of insulin receptor gene influences insulin resistance in PCOS: a pilot study on North Indian women. Biochem Genet. 2016;54:158-68.
15. Chen ZJ, Shi YH, Zhao YR, Li Y, Tang R, Zhao LX, et al. Correlation between single nucleotide polymorphism of insulin receptor gene with polycystic ovary syndrome. Zhonghua Fu Chan Ke Za Zhi. 2004;39:582-5.
16. Bodhini D, Sandhiya M, Ghosh S, Majumder PP, Rao MR, Mohan V, et al. Association of His1085His INSR gene polymorphism with type 2 diabetes in South Indians. Diabetes Technol Ther. 2012;14:696-700.
17. Sokhi J, Sikka R, Raina P, Kaur R, Matharoo K, Arora P, et al. Association of genetic variants in INS (rs689), INSR (rs1799816) and PP1G.G (rs1799999) with type 2 diabetes (T2D): a case-control study in three ethnic groups from North-West India. Mol Genet Genomics. 2016;291:205-16.
18. Brunt EM, Janney CG, Di Bisceglie AM, Neuschwander-Tetri BA, Bacon BR. Nonalcoholic steatohepatitis: a proposal for grading and staging the histological lesions. Am J Gastroenterol. 1999;94:2467-74.
19. Salamone F, and Bugianesi E. Nonalcoholic fatty liver disease: the hepatic trigger of the metabolic syndrome. J Hepatol. 2010;53:1146-7.
20. Atay K, Canbakan B, Koroglu E, Hatemi I, Canbakan M, Kepil N, et al. Apoptosis and disease severity is associated with insulin resistance in non-alcoholic fatty liver disease. Acta Gastroenterol Belg. 2017;80:271-7.
21. Fujii H, Imajo K, Yoneda M, Nakahara T, Hyogo H, Takahashi H, et al. HOMA-IR: An independent predictor of advanced liver fibrosis in nondiabetic non-alcoholic fatty liver disease. J Gastroenterol Hepatol. 2019;34:1390-5.
22. Dongiovanni P, Valenti L, Rametta R, Daly AK, Nobili V, Mozzi E, et al. Genetic variants regulating insulin receptor signaling are associated with the severity of liver damage in patients with non-alcoholic fatty liver disease. Gut. 2010;59: 267-73.
23. Michael MD, Kulkarni RN, Postic C, Previs SF, Shulman GI, Magnuson MA, et al. Loss of insulin signaling in hepatocytes leads to severe insulin resistance and progressive hepatic dysfunction. Mol Cell. 2000;6:87-97.
24. Taylor SI, Kadowaki T, Kadowaki H, Accili D, Cama A, McKeon C. Mutations in insulin-receptor gene in insulin-resistant patients. Diabetes Care.1990;13:257-79.
25. Conne B, Stutz A, Vassalli JD. The 3' untranslated region of messenger RNA: a molecular "hotspot" for pathology? Nat Med. 2000;6:637-41.
26. Malodobra M, Pilecka A, Gworys B, Adamiec R. Single nucleotide polymorphisms within functional regions of genes implicated in insulin action and association with the insulin resistant phenotype. Mol Cell Biochem. 2011;349:187-93.
27. Seino S, Seino M, Bell GI. Human insulin receptor gene: partial sequence and amplification of exons by polymerase chain reaction. Diabetes. 1990;39:123-8.
28. Moller DE, Yokota A, White MF, Pazianos AG, Flier JS. A naturally occurring mutation of insulin receptor alanine 1134 impairs tyrosine kinase function and is associated with dominantly inherited insulin resistance. J Biol Chem. 1990;265:14979-85.
29. Kimchi-Sarfaty C, Oh JM, Kim IW, Sauna ZE, Calcagno AM, Ambudkar SV, et al. A silent polymorphism in the MDR1 gene changes substrate specificity. Science. 2007;315:525-8.
30. Skrgatić L, Baldani DP, Gersak K, Cerne JZ, Ferk P, Corić M. Genetic polymorphisms of INS, INSR and IRS-1 genes are not associated with polycystic ovary syndrome in Croatian women. Coll Antropol. 2013;37:141-6.
31. Siegel S, Futterweit W, Davies TF, Concepcion ES, Greenberg DA, Villanueva R, et al. A C/T single nucleotide polymorphism at the tyrosine kinase domain of the insulin receptor gene is associated with polycystic ovary syndrome. Fertil Steril. 2002;78:1240-3.
32. Al-Share QY, DeAngelis AM, Lester SG, Bowman TA, Ramakrishnan SK, Abdallah SL, et al. Forced hepatic overexpression of CEACAM1 curtails diet-induced insulin resistance. Diabetes. 2015;64:2780-90.
33. Prudente S, and Trischitta V. The pleiotropic effect of the ENPP1 (PC-1) gene on insulin resistance, obesity, and type 2 diabetes. J Clin Endocrinol Metab. 2006;91:4767-8.
34. Kuroda A, Rauch TA, Todorov I, Ku HT, Al-Abdullah IH, Kandeel F, et al. Insulin gene expression is regulated by DNA methylation. PloS One. 2009;4:e6953.

ORIGINAL ARTICLE

AG-2020-29
doi.org/10.1590/S0004-2803.202000000-40

Normal values of esophageal high-resolution manometry: a Brazilian multicenter study

Gerson Ricardo **DOMINGUES**[1], Nelson Henrique **MICHELSOHN**[2,3], Ricardo Guilherme **VIEBIG**[4], Décio **CHINZON**[5], Ary **NASI**[3,6], Carla Granja **ANDRADE**[7], Eponina Maria **LEMME**[8], Luiz João **ABRAHÃO JUNIOR**[8], Mauricio Gustavo **BRAVIM**[9], Miguel Ângelo **NOBRE-E-SOUZA**[10], Nayara Salgado **CARVALHO**[11], Paulo J P C **CARVALHO**[11], Tomás Navarro **RODRIGUES**[12] and Joaquim Prado P **MORAES FILHO**[13]

Received: 3 March 2020
Accepted: 30 March 2020

ABSTRACT – **Background** – The high-resolution manometry has been a significant advance in esophageal diagnostics. There are different types of catheter and systems devices to capture esophageal pressures that generate variable data related to Chicago Classification (CC) and consequently influence normal values results. There are not normative data for the 24-channel water-perfused high-resolution manometry system most used in Brazil with healthy volunteers in supine posture. **Objective** – To determine manometric esophageal normative values for a 24-channel water-perfused high-resolution manometry catheter in supine posture using healthy volunteers according to CC 3.0 parameters. **Methods** – A total of 92 volunteers with no gastrointestinal symptoms or medications affecting GI motility underwent esophageal high-resolution manometry by standard protocol. Age, gender and manometry parameters analyzed using Alacer software were collected. The median, range, and 5th and 95th percentiles (where applicable) were obtained for all high-resolution manometry metrics. Normal value percentiles were defined as 95th integrated relaxation pressure, 5th–100th distal contractile integral, and 5th distal latency. **Results** – The mean age was 40.5±13.2 years. Our normative metrics were integrated relaxation pressure <16 mmHg and distal contractile integral (708–4111 mmHg.cm.s) distal latency was <6 s and peristaltic break size (<4.0 cm). For EGJ-CI the range 5th–95th was 21.7–86.9 mmHg.cm.s. **Conclusion** – This is the first report of normative data for the 24-channel water-perfused system in supine posture. It revealed higher integrated relaxation pressure and distal latency duration which suggest the need to change CC 3.0 cutoffs for this system. It is observed that there is a tendency that DCI >7000 mmHg.cm.s may represent the lower limit of hypercontractility, and when <700 mmHg.cm.s (<5% percentile) interpreted as ineffective esophageal motility or failcontraction. Also compared to Chicago 3.0, higher integrated relaxation pressure and duration of distal latency were found. We emphasize that these data must be confirmed by future studies.

HEADINGS – Esophagus. Gastrointestinal motility. Manometry. Peristalsis. Reference values.

Keypoints

- Chicago Classification 3.0 metrics were derived from solid-state catheters. Brazilian multicenter normative data using a 24-channel water-perfused high-resolution manometry catheter is not available.
- Pressure-dependent Chicago Classification metrics, integrated relaxation pressure, distal latency and distal contractile integral are higher with the 24-channel water-perfused system.
- This is the first multicenter study reporting esophageal normal values for the 24-channel water-perfused high-resolution manometry system widely used in Brazil.

INTRODUCTION

Esophageal motility evaluation has long been an important tool to clarify patient's motor esophageal symptoms. More recently, the introduction of high-resolution manometry (HRM) has made important changes in the understanding of pathophysiologic mechanisms and allowed the creation of sophisticated analysis algorithms, placing this diagnostic method to a new level[1]. Actually, it provides image-based manometric interpretation with significant advantages over conventional manometry and, in addition, HRM has also been proved friendly use, easy to learn, improved patient comfort and diagnostic yield[1].

Two types of HRM systems are currently available: water-perfused HRM and solid-state HRM[2]. Both systems have more and closer pressure sensors than the conventional manometry, and the pressure topography used in the HRM gives detailed information of the whole esophagus and parts of the pharynx and the stomach. However, HRM data derived from both systems may vary and are influenced and depend on the perfusion rate, catheter diameter and solid-state sensors that has electronic pressure sensors within the catheter itself[3].

Declared conflict of interest of all authors: none
Disclosure of funding: no funding received
All authors are from Brazilian Working Group for Esophageal High Resolution Manometry.
[1] Universidade do Estado do Rio de Janeiro, Departamento de Medicina Interna, Disciplina de Gastroenterologia, Rio de Janeiro, RJ, Brasil. [2] Centro de Motilidade Digestiva (CDM), São Paulo, SP, Brasil. [3] Fleury Medicina e Saúde, Departamento de Motilidade, São Paulo, SP, Brasil. [4] Instituto Brasileiro de Estudos e Pesquisas de Gastroenterologia e Especialidades (IBEPEGE), Motilidade Digestiva e Neurogastroenterologia (MoDiNe), São Paulo, SP, Brasil. [5] Universidade de São Paulo, Faculdade de Medicina, Hospital das Clínicas, São Paulo, SP, Brasil. [6] Universidade de São Paulo, Departamento de Motilidade, São Paulo, SP, Brasil. [7] CGA Centro Especializado em Neurogastroenterologia e Motilidade Digestiva, São Paulo, SP, Brasil. [8] Universidade Federal do Rio de Janeiro, Hospital Universitário Clementino Fraga Filho, Clínica Médica, Rio de Janeiro, RJ, Brasil. [9] Centro de Motilidade do Aparelho Digestivo (CEMAD), Belo Horizonte, MG, Brasil. [10] Universidade Federal do Ceará, Faculdade de Medicina, Fortaleza, CE, Brasil. [11] Hospital Israelita Albert Einstein, Núcleo de Fisiologia Gastrointestinal (NUFIG), São Paulo SP, Brasil. [12] Universidade de São Paulo, Faculdade de Medicina, Hospital das Clínicas, Serviço de Gastroenterologia e Hepatologia Clínica, São Paulo, SP, Brasil. [13] Universidade de São Paulo, Faculdade de Medicina, Departamento de Gastroenterologia São Paulo, SP, Brasil.
Corresponding author: Gerson Domingues. E-mail: gersondomingues62@gmail.com

Using different HRM systems, investigators have been trying to set up a reasonable and systemic criterion for the diagnosis of the esophageal motility diseases[3]. Meanwhile, the closer pressure sensors allow HRM systems provide more detailed and precise manometry results than conventional manometry systems[4]. Thus, with the use of this technique, an HRM solid-state catheter was developed that showed a high level of detail at the esophagogastric junction (EGJ) and the esophagus by using 36 pressure sensors. The currently available solid-state HRM catheters often use circumferential pressure sensors, and it has been suggested that those pressure sensors increase the accuracy of measuring the pressure of the asymmetric EGJ[5]. Furthermore, the response rate of solid-state manometry is considerably higher.

Normal HRM values for Western populations, in particular North Americans, were first established for the solid-state system and a new classification, Chicago Classification (CC)[5] was developed. Solid-state HRM features an easier system setup and faster response rates than water-perfused HRM systems, but from a practical point of view, the cost of solid state HRM devices poses a limitation for its generalized use[6]. Water-perfused HRM systems are still frequently used in many European, Asian Pacific, and South America countries because of their better durability and the lower cost of the catheter and associated pressure transduction system[6]. Although perfusion catheters require considerable preparation time, the new catheters that have recently been developed, obtaining pressure measurements, have quality comparable to solid-state HRM[7,8]. Normal values for water-perfused HRM for the Western population have thus also been established with only slight differences from the previously published values for solid-state HRM[8].

The solid-state manometry catheter is currently considered the gold standard for esophageal HRM, and the normal values presented in CC have therefore been developed specifically for the use of solid-state catheters[9,10]. Currently, several different HRM systems are commercially available and new types of catheters are being developed as the clinical importance of esophageal manometry is now clearly established. In this way, normative values for esophageal HRM using different systems are important and needed. However, today, these data are still scarse. The International High-Resolution Manometry Working Group recommends that CC parameter normative values be determined for each system and population, with modification if different from their recommendation[10].

In view of the above considerations, the aim of the present study was to establish normal reference values for the 24-channel water-perfused HRM system in a sample of the Brazilian population.

To obtain an expressive result, the Brazilian Working Group for Esophageal High-Resolution Manometry was constituted and carried out this project under the supervision of the Brazilian Society of Digestive Motility and Neurogastroenterology.

METHODS

Study subjects

This prospective study on healthy volunteers was a multicenter study that enrolled eight Brazilian known gastrointestinal motility units, between January 2018 and June 2019.

The project received approval from *Hospital Universitário Pedro Ernesto* (UERJ) Research Ethics Committee under the reference of CAAE 07672818.7.0000.5259.

The healthy asymptomatic volunteers aged ≥18 years were recruited among hospital employees ranging from domestic staff to doctors/senior managers as well as non-hospital volunteers. All signed a written informed consent for study participation before undergoing the test.

The exclusion criteria were as follow:

- No history of digestive disorders and no other illnesses, such as systemic sclerosis, diabetes mellitus, connective tissue diseases, liver cirrhosis, malignancy.
- No gastrointestinal symptoms in the previous six months.
- Recent ingestion of medications that may affect gastrointestinal motility such as calcium channel blockers, nitrates, domperidone or opioids.
- Use of anticoagulants or antiplatelets in one week prior to enrollment in the study.
- History of acute inflammation or stricture or obstruction of the nasal cavity or esophagus.

Equipment

All studies were performed with Alacer Multiplex System which consists:

A 24-channel water-perfused PVC esophageal catheter of 4.7 mm in outer diameter was used. The esophageal catheter includes 24 pressure channels distributed along the catheter. Each channel is connected to an external transducer that registers pressure changes.

A continuous flow of water with constant pressure and speed is generated through the catheter by a perfusion pump. The luminal diameter of each perfusion channel was 0.43 mm, oriented spirally, with 10 sensors spaced at 0.7 cm placed in the zone recording the EGJ and spaced 2 cm apart in the areas of the esophageal body, covering a total length of 34 cm (FIGURE 1).

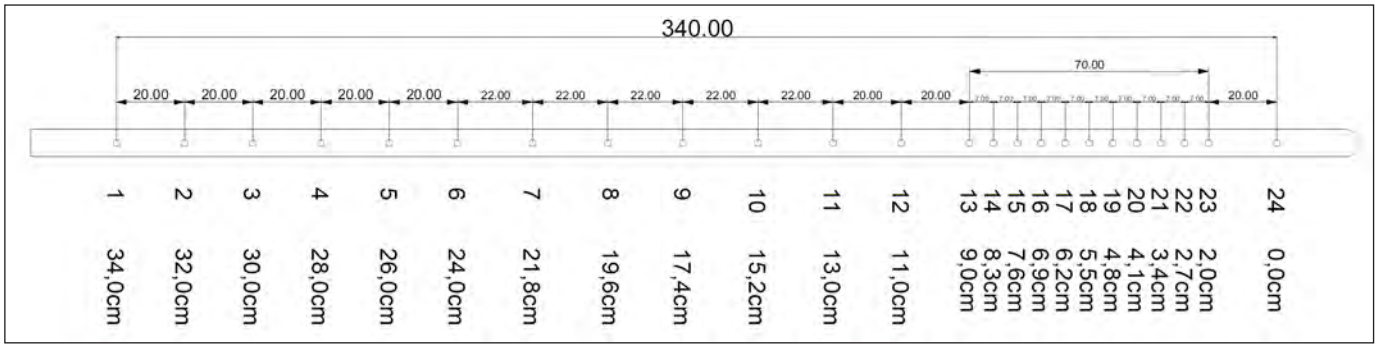


FIGURE 1. Schematic representation of water-perfused high-resolution manometry catheter with the spiral configuration of the pressure sensors to measure esophagogastric junction.

Data obtained through this system was later analyzed with a dedicated software (Alacer HRM – Alacer Biomédica Indústria Eletrônica, São Paulo, Brazil). This allows to measure the EGJ relaxation with all its components (lower esophageal sphincter (LES), crural diaphragm, intrabolus pressure) and body of the esophagus contractility[6].

Study protocol

All participants provided basic demographic information and were interviewed by a gastroenterologist. After an ≥4 hour fast and a detailed explanation and reassurance regarding the procedure, subjects underwent a HRM study performed by one of the authors listed. For each HRM study, the manometry catheter was introduced trans nasally and when the catheter tip was inserted near the depth of the esophageal inlet, the participants were asked to swallow sips of water to facilitate the passage of the catheter into the esophagus, and then it was positioned to record from hypopharynx to stomach with the three distal sensors positioned in the gastric lumen.

After successful catheter insertion to a depth of approximately 45–50 cm, as identified by the presence of both upper and lower high-pressure zones (upper esophageal sphincter – UES and LES), the participants then assumed a supine position and were allowed five minutes for accommodation. The catheter was zeroed to intragastric pressure. Then, patients received 10 boluses of 5 mL of water with an interval of 20 s. All swallows were revised by three investigators and inter-reader concordance >90% had been established, after standardizing the reading protocol among the three readers as part of clinical governance standards in routine clinical care.

HRM data was analyzed according to the algorithm recommended by the Chicago Classification[10]. The basal and relaxation LES pressures were referenced to gastric pressure, whereas the esophageal contraction parameters and UES pressures were referenced to atmospheric pressure.

Manometric parameters of the UES (upper esophageal sphincter resting pressure, upper esophageal sphincter extension), of the esophagus body (distal contractile integral, distal contraction latency, esophageal length) and of the EGJ (LES resting pressure, integrated relaxation pressure 4-second, LES extension, EGJ contractile integral) were determined.

The UES resting pressure was automatically recorded after the placement of specific software markers on the UES outline during a period of no swallowing. The contractile deceleration point was taken as the inflection point along the 30 mmHg isobaric contour where propagation velocity slows, demarcating the phrenic ampulla. The distal latency (DL) was defined as the interval of time between the deglutition UES relaxation and the contractile deceleration point. The distal contractile integral (DCI) was calculated by multiplying the mean pressure (amplitude) by the duration of propagation of the contractile wave front by the length of smooth muscle esophagus from the body transition zone until the distal pressure trough, excluding pressures below 20 mmHg (FIGURE 2). Esophageal body length was defined as the distance between the lower border of the UES and the upper border of the LES.

The basal lower esophageal sphincter median respiratory resting pressure was automatically determined by placing the specific marker over the EGJ outline during a period of no swallowing. The 4s integrated relaxation pressure (IRP-4s) was defined as the mean EGJ relaxation lowest cumulative pressures during 4s, continuous and/or separated, during a 10-second period post deglutition time window following the relaxation of the UES in the anatomic zone defining EGJ. The IRP is referenced to gastric pressure, while all other metrics are referenced to the atmospheric pressure. FIGURE 2.

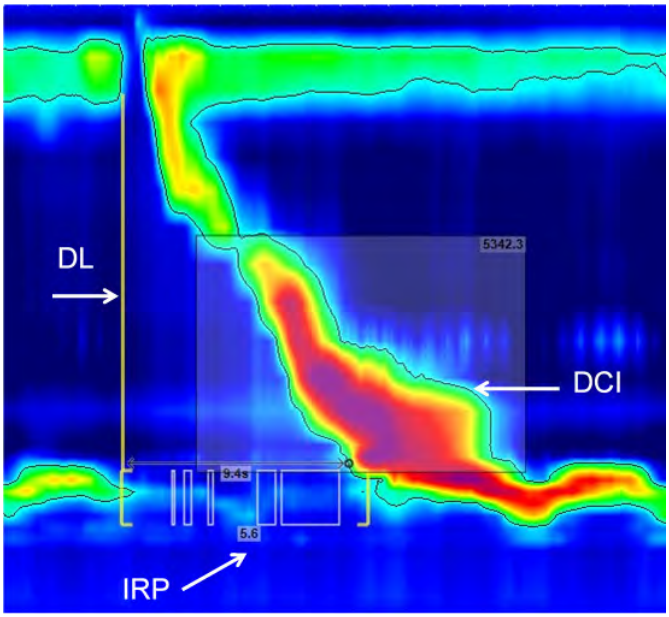


FIGURE 2. Record of a deglutition captured by high-resolution manometry water-perfused system device showing the markings of the traditional Chicago Classification parameters, isobaric contour 20 mmHg. High-resolution manometry parameters as determined by Chicago Classification. DL: distal latency; DCI: distal contractile integral; IRP: integrated relaxation pressure.

The EGJ contractile integral (EGJ-CI) is a novel esophageal high-resolution manometry (HRM) metric that evaluates EGJ barrier function[11]. The EGJ-CI takes both inspiratory and expiratory LES pressures, and EGJ length into account, as all are fundamental to the assessment of the EGJ barrier. The landmark period was used to identify three respiratory cycles, and the duration of the cycles was recorded. The gastric baseline was determined during the landmark phase and set as the threshold for EGJ-CI calculation. The value computed with the DCI tool in mmHg.cm.s was then divided by the duration of the three respiratory cycles (in seconds) yielding EGJ-CI units of mmHg.cm. Hence, although time is not a factor in EGJ-CI units, the measure does reflect the contractility of the EGJ for a period of three respiratory cycles[11]. FIGURE 3.

To all HRM metrics was used a 20 mmHg isobaric contour which was also used in the CC. Normative values for each of the above parameters were derived as follows:

a: The mean, median, range, and percentiles (5th and 95th) were obtained for all the above HRM metrics.

b: The percentiles used as cutoff values were:

1. IRP-4s: Less than 95th percentile.
2. DL: 5th percentile value.
3. DCI: 5th-95th percentile.
4. DCI-CI: 5th percentile value.
5. Peristaltic break size: 95th percentile.

Statistical analysis

Data were expressed by measures of central tendency and dispersion. Statistical analysis was performed using SPSS version 26

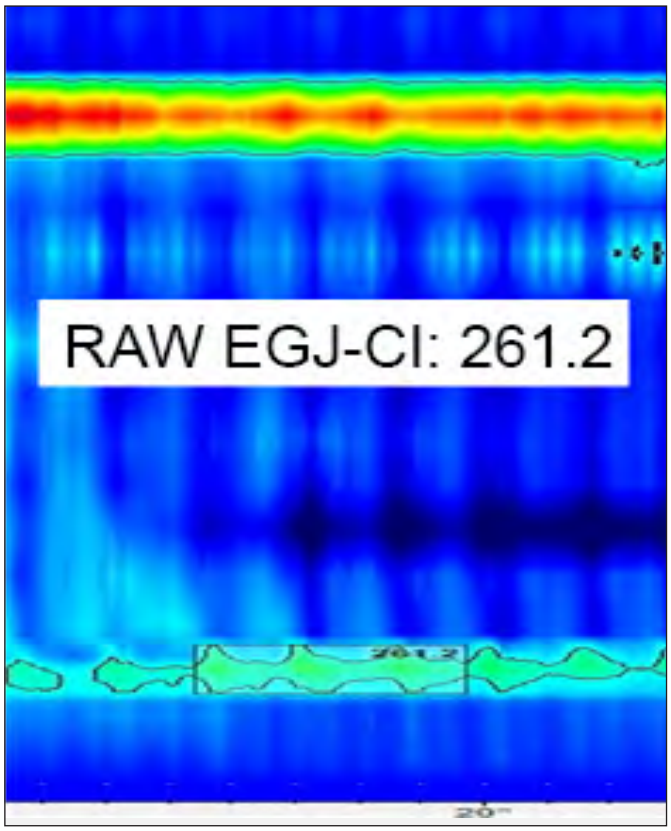


FIGURE 3. Esophagogastric junction contractile integral calculation (EGJ-CI). The EGJ-CI takes both inspiratory and expiratory lower esophageal sphincter pressures, and EGJ length into account, as all are fundamental to the assessment of the EGJ barrier. The landmark period was used to identify three respiratory cycles, and the duration of the cycles was recorded. The gastric baseline was determined during the landmark phase, and set as the threshold for EGJ-CI calculation. The value computed with the distal contractile integral tool in mmHg.cm.s was then divided by the duration of the three respiratory cycles (in seconds) yielding EGJ-CI units of mmHg.cm.

(SPSS, Inc Chicago, IL, USA). The mean value ±SD, the median (interquartile), median and the 5th and 95th percentiles were calculated for each parameter. Reference values were established as the interval between the 5th and 95th percentiles of values.

RESULTS

Subjects

The HRM procedure was well tolerated by the participants of the study, 92 heathy volunteers (51 female and 41 male), that were enrolled for analysis. The mean age was 40.5±13.2 years (range: 18–75years).

Measurements were successfully obtained in all subjects, and none of them met criteria for major esophageal motor disorders as stated by CC.

Normative values for water-perfused HRM

No participants had hiatal hernia. EGJ, esophageal, and UES parameters are shown in TABLE 1.

EGJ

For the mean basal pressure of the EGJ the 5th–95th percentile range was 13.7–42.4 mmHg (range: 7.2–57 mmHg). For the extension of EGJ the 5th-95th range was 2.0–4.6 cm (range: 1.9–5.3 cm). The 5th–95th percentile range for the IRP- 4s was 4.5–15.8 mmHg (range: 2.6–17.8 mmHg). For EGJ-CI the 5th–95th was 21.7–86.9 mmHg.cm.s (range: 9.8–126.1 mmHg.cm.s).

Esophageal body

The 5th–95th percentile range was 708–4,111 mmHg.cm.s for DCI (range: 464.8-6839 mmHg.cm.s), and 5.8–9.9 s for DL (range: 5.3–10.7s). Total break size in the esophageal contraction length was 4.0 cm (range: 0.1–6.8 cm).

UES

The 5th–95th percentile range was 25.9–145.8 mmHg for mean basal pressure of the UES (range: 21.3–198.3 mmHg), and 2.3–5.2 mmHg for UES extension (range: 2.0–5.7 cm).

TABLE 1. EGJ parameters, esophageal parameters, and UES parameters as measured by water-perfused HRM in 92 healthy volunteers.

			Percentiles	
	Mean ±SD	Median (IIQ)	5th	95th
EGJ parameters				
Basal pressure (mean), mmHg	24.9±8.8	23.2 (18.7–29.6)	13.7	42.4
Extension	3.1±0.7	3.1 (2.6–3.7)	2.0	4.6
IRP, 4s	9.4±3.6	8.8 (6.7–11.9)	4.5	15.8
EGJ-CI	48.1±19.3	45.8 (34.3–59)	21.7	86.9
Esophageal parameters				
DCI, mmHg.cm.s	2169±1097	1938 (1383–2745)	708	4111
DL, s	7.5±1.1	7.4 (6.7–8.1)	5.8	9.9
Total break length, cm	1.3±1.3	0.8 (0.4–2.1)	0.1	4.2
UES parameters				
Basal pressure (mean), mmHg	66.7±37.7	56.3 (36.6–85.8)	25.9	145.8
Extension	3.5±0.8	3.4 (3.0–3.8)	2.3	5.2

EGJ: esophagogastric junction; IRP: integrated relaxation pressure; ECJ-CI: contractile integral of esophagogastric junction; DCI: distal contractile integral; DL: distal latency; UES: upper esophageal sphincter.

In brief, normative values for water-perfused HRM of the CC were as follow:

IRP: <16.0 mmHg

EGJ-CI: >22.0 mmHg.cm

DCI: 700–4.100 mmHg.cm.s (normal); Ineffective esophageal motility: <700.0 mmHg; Hypercontractile: >7000.0 mmHg.cm.s

DL: <6.0s

Peristaltic break size: <4.0 cm

DISCUSSION

Esophageal HRM is today considered worldwide as a first class exam. The CC 3.0 for esophageal motility disorders is based on a set of normative values for key metrics that was obtained using one of the commercially available HRM devices[10]. Thus, it is of great importance to evaluate whether these normative values can be used for different HRM devices as well. It should be considered that numerous factors including the type of HRM system, demographic factors, catheter diameter, body position during testing, consistency of bolus swallows, and esophageal length have an influence on the normative data[12]. On the other hand, there are HRM different systems and types of catheters commercially available that should have their results clinically evaluated as HRM has becoming an important tool to approach esophageal motor disorders.

HRM systems led to the establishment of new parameters specially to study the EGJ and esophageal body and hence new algorithms of analysis[10]. In this regard, HRM water-perfused systems deserve some additional comments related to limitations and advantages such as set up and preparation of the device is more time-consuming and pressure responses rates are slower compared do solid-state systems. On the other hand, as catheters of the water-perfused systems tend to be more durable and comfortable and even cheaper than the solid-state devices[12], the HRM water-perfused devices are widely used in emerging countries like Brazil. In this regard, it should be mention a prospective, randomized, double blind, crossover study comparing the tolerability and procedure duration of a 36-channel solid-state system (Given Imaging, Los Angeles, CA, USA) with that of a 24-channel water-perfused system (EB Neuro, Firenze, Italy) in 20 healthy volunteers[13]. No difference in tolerability between the two systems was observed. Although the water-perfused procedure required a significantly higher set-up and analysis time compared to the solid-state HRM, no difference between the two was observed in terms of tracing acquisition time[13].

The spatial resolution of the catheter used on our HRM water-perfused system was 2 cm spacing in esophageal body and 0.7 cm spacing in EGJ zone (7 cm segment). It is an important issue as spatial resolution could have an effect on the CC metrics and diagnosis. De Schepper et al.[14] conducted a study in 20 healthy volunteers and 47 patients with upper gastrointestinal symptoms and they reanalyzed HRM studies of the esophagus using the original 1 cm spacing in the segments outside the 7 cm EGJ segment, and again after manually increasing the spacing between sensors to 2, 3, and 4 cm above the LES region. There was a very strong correlation between the 1 cm and 2 cm analysis for all Chicago metrics studied in healthy volunteers and the 2 cm spacing analysis also correlated very well with the 1 cm analysis for the different Chicago diagnoses obtained in the patients. Thus, the same normal values of CC can be used when catheters with a slightly lower resolution are used[14]. Therefore, considering these data, we assume that our 24-channel water-perfused catheter with its unique spiral configuration to study EGJ region with sensors spaced 7 cm and spaced 2 cm apart in the area of the esophageal body is a reliable configuration to establish normal values.

The ECJ contractile integral is a novel HRM tool designed to assess EGJ barrier function, which incorporates an intragastric pressure reference and the respiratory cycle to assess the barrier function of the EGJ[15]. Reduced EGJ-CI was initially reported to be associated with gastroesophageal reflux disease[15]. A greater-than-normal EGJ-CI was reported in patients with newly diagnosed achalasia[16] and, recently, this metric of EGJ has been used to assessment of treatment response in achalasia[17]. To the best of our knowledge, this study is the first prospective work with HRM water-perfused manometry that assessed EGJ-CI normative values (TABLE 1).

Some handicaps were found in the study of UES opening and its residual pressure. Since the UES is composed of striated muscle, pressure changes are more rapid than pressure changes in the esophageal body or in the EGJ. The slower response rate of HRM water-perfused is likely the cause of the large differences and poor agreement between the UES residual pressure as measured by solid-state HRM and water-perfused HRM[9]. Another reason for differences in UES parameters might be the existence of the pharyngo-UES reflex. It has been shown that both rapid and continuous slow perfusion of the pharynx with water can increase UES pressure[9]. For these reasons, we believe that HRM water-perfused might overestimate UES resting pressure and UES relaxation pressure and, consequently, water-perfused HRM is not appropriate to measure residual pressure of the UES.

In our study, like others[6,8,12,18-23], normal values were defined, dependent on what parameter studied, by the 5th and/or 95th percentile obtained in a population of healthy volunteers. Keeping in mind that this statistical analysis of results can induce, depending on the parameter, to a false abnormal result, simply by chance (5% or 10%). The maximal DCI of the healthy individuals in this study was 6839 mmHg.cm.s in water swallows, so 7000.0 mmHg.cm.s is probably the proper threshold of the DCI for the diagnosis of hypercontractile swallow in this studied population. Jackhammer esophagus diagnosis can be proposed as DCI >7000.0 m mmHg.cm.s in ≥2 swallows. In this regard, data must be interpreted carefully by physicians, always in the context of the clinical presentation, to avoid judgment biases.

In our study DCI values were lower than those in CC 3.0[10]. One explanation for this discrepancy is that we used intragastric pressure as zero value, as opposed to atmospheric pressure when solid state catheters are used[24], and in this study, intragastric pressure was 5 mmHg. Another explanation, we supposed to be a slower increase in pressures due to higher complacency of our system. This can also explain the longer DL.

Kuribayashi et al.[25] studied a Japanese population and used DCI >10,000 mmHg.cm.s as threshold for hypercontractile contraction and <1,000 mmHg.cm.s as threshold for weak contraction. In the present work, we suggest a DCI <700.0 mmHg.cm.s to define weak contraction, and in ≥50% of swallows to define ineffective esophageal motility. We must be careful in this respect, since the threshold of <450 mmHg.cm.s in CC 3.0 was not derived from their data but is a number that roughly correlates with an amplitude <30 mmHg in conventional manometry. Thus, this topic deserves further studies.

Recently, Da Silva et al.[18] published a Brazilian unicenter

cohort study to evaluate normative values for HRM that used the same water-perfused device as ours, but with some differences in the protocol study as long as the number of volunteers were significantly smaller, catheter configuration was different, and subjects underwent HRM with the test performed in left lateral decubitus that probably concurred to some discrepancies observed in IRP-4s, DL and DCI calculation.

Routinely the esophageal motility function is tested with liquid bolus swallows. Although there are efforts to improve esophageal motility testing and diagnosis with solid bolus swallows[19,23,26], lack of standardization of the method and appropriate algorithm analysis preclude its use in clinical practice. As such, in the present study only liquid bolus swallows to determine normative values, were used.

The analysis of the results of normative values among various different configuration catheters for HRM water-perfused systems including our study (TABLE 2), shows some discrete discrepancies for the most relevant CC HRM parameters and reinforce the need to set normal values for each device configuration in order to support the use of this technique in the diagnostic work-up of patients with dysphagia amongst others. However, the usefulness of normal values is always determined by the likelihood that an abnormal value can indeed be considered pathological and responsible for symptoms[12], and in this context, clinical evaluation continue to be an important issue in decision making. Esophageal HRM is an evolving method and the next version (4.0) is expected to include a new protocol, recommending routine provocative testing prior to surgical fundoplication[27].

While the strength of our study is the cohort size, its limitations include lack of subjects in extremes of age. Furthermore, the water-perfused system was not compared head-to-head with a solid-state system due to high cost issues.

In conclusion, this is the first multicenter study that reported esophageal normative data in supine posture for the 24-channel water-perfused HRM system, the most common used in Brazil. Appropriated modifications of CC cutoff values were made and the normal values proposed here are slightly different from previously obtained normal values ascertained by other HRM water-perfused systems. The presented normal values actually helps the physicians to use this HRM water-perfused in clinical practice and to define their normal and abnormal values.

The results of our study also confirm that differences in measurement outcome exist between different systems and that normal values must be determined for each different manometric system. It is essential an effort from others motility labs worldwide, using the various esophageal HRM systems configurations, to publish their data in order to validate normative values and make the valuable CC relevant for all.

Authors' contribution

Domingues GR, Michelsohn NH, Viebig RG: conception and design of the study, data interpretation, critical revision of manuscript, data collection, text writing. Chinzon D, Moraes-Filho JPP: critical revision of manuscript, text writing. Nasi A, Andrade CG, Lemme EM, Abrahão Junior LJ, Bravim MG, Nobre e Souza M, Carvalho NS, Carvalho PJPC, Rodrigues TN: data collection.

Orcid

Gerson Ricardo Domingues: 0000-0003-0431-451X.
Nelson Henrique Michelsohn: 0000-0003-3394-7172.
Ricardo Guilherme Viebig: 0000-0002-6541-0401.
Décio Chinzon: 0000-0003-3030-6687.
Joaquim Prado P Moraes Filho: 0000-0003-1280-6047.
Ary Nasi: 0000-0001-6928-4281.
Carla Granja Andrade: 0000-0002-5859-0539.
Eponina Maria Lemme: 0000-0002-1916-9274.
Luiz João Abrahão Junior: 0000-0003-2107-2460.
Mauricio Gustavo Bravim: 0000-0002-6268-4060.
Miguel Ângelo Nobre e Souza: 0000-0003-3446-739X.
Nayara Salgado Carvalho: 0000-0001-9167-8957.
Paulo J P C Carvalho: 0000-0002-9041-8835.
Tomás Navarro Rodrigues: 0000-0002-3458-699X.

TABLE 2. Studies of normative values reported for supine posture in healthy volunteers using water-perfused systems.

Study	Catheter (channels)	Diameter (cm)	n volunteers (Country)	BERP (5th–95th) mmHg	IRP-4s (mmHg)	DCI (5th–95th) mmHg.cm.s	DL (5th) s	ECJ-CI (5th) mmHg.cm.s
Current study	24 perfusion	4.7	92 (Brazil)	13.7 / 42.4	15.8	708-4111	5.8	21.7
Silva/Herbella[18]	24 perfusion	4.7	32 (Brazil)	4.9 / 37	16	83-3837	6.2	–
Srinivas[20]	16 perfusion	3.5	53 (India)	4.4 / 37.6	13	72-3276	4.6	–
Burgos-Santamaria[6]	22 perfusion	4	16 (Spain)	5 / 54	20	285-2820	6.1	–
Tseng[21]	22 perfusion	4.2	66 (Taiwan)	8.7 / 46.5	20	99-2816	6.2	–
Capovilla[13]	24 perfusion	–	20 (Italy)	4 / 34.3	8.8	557-1726	7	–
Kessing[8]	36 perfusion	4.7	50 (Holland)	3 / 29.8	18.8	142-3674	6.2	–

BERP: basal EGJ respiratory pressure; IRP-4s: integrated relaxation pressure; DL: distal latency; DCI: distal contractile integral; ECJ-CI: contractile integral of esophagogastric junction.

Domingues G, Michelsohn NH, Viebig RG, Chinzon D, Moraes-Filho JPP, Nasi A, Andrade CG, Lemme EM, Abrahão-Junior LJ, Bravim MG, Nobre-e-Sousa MA, Carvalho NS, Carvalho PJPC, Rodrigues TN. Valores normais da manometria de alta resolução de esôfago: estudo multicêntrico brasileiro. Arq Gastroenterol. 2020;57(2):209-15.

RESUMO – **Contexto** – A manometria de alta resolução tem sido um avanço significativo nos diagnósticos esofágicos. Existem diferentes tipos de cateteres e sistemas dispositivos para capturar pressões esofágicas que geram dados variáveis relacionados à Classificação de Chicago (CC) e, consequentemente, podem influenciar os resultados de valores da normalidade. Não há dados normativos com voluntários saudáveis na postura supina, para o sistema manométrico sob perfusão em água de 24 canais, o mais utilizado no Brasil. **Objetivo** – Determinar os valores normativos manométricos do esôfago para um cateter sob perfusão de alta resolução de 24 canais na postura supina utilizando-se voluntários saudáveis assintomáticos de acordo com os parâmetros CC. **Métodos** – Um total de 92 voluntários sem sintomas gastrointestinais ou medicamentos que afetassem a motilidade gastrointestinal foram submetidos à manometria de alta resolução do esôfago por protocolo padrão (Sistema Alacer Multiplex). Foram coletados parâmetros de idade, sexo e os da manometria analisados pelo software Alacer versão 6.2. A mediana, os limites, e 5% e 95% percentis (quando aplicável) foram obtidos para todas as métricas de alta resolução. Os valores normais foram definidos como percentis de 95% da integral da pressão de relaxamento (IRP), 5%–100% da integral contrátil distal (DCI), e 5% latência distal. **Resultados** – A média de idade foi de 40,5±13,2 anos. As métricas normativas foram definidas como IRP <16 mmHg) e DCI (708–4111 mmHg.cm.s). Para a latência distal foi de 5,8–9,9 s (faixa: 5,3–10,7s). O comprimento total de quebra na contração esofágica foi de 4,0 cm (faixa: 0,1–6,8 cm). Para a EGJ-CI a faixa 5%–95% percentis foi de 21,7–86,9 mmHg.cm.s. **Conclusão** – Este é o primeiro relatório de dados normativos para o sistema de 24 canais perfundido por água na postura supina. A partir dos dados encontrados observa-se a possibilidade de alterar os cortes CC 3.0 para este sistema. Observa-se que há uma tendência que DCI >7000 mmHg.cm.s possa representar o limite inferior da hipercontratilidade e quando <700 mmHg.cm.s (<5% percentil) interpretada como motilidade esofágica ineficaz ou contração falha. Também em comparação com Chicago 3.0, foi encontrada maior pressão de relaxamento integrado e duração da latência distal. Ressaltamos que esses dados devem ser confirmados por estudos futuros.

DESCRITORES – Esôfago. Motilidade gastrointestinal. Manometria. Peristaltismo. Valores de referência.

REFERENCES

1. Niebisch S, Wilshire CL, Peters JH. Systematic analysis of esophageal pressure topography in high-resolution manometry of 68 normal volunteers. Dis Esophagus. 2013;26:651-60.
2. Zavala-Solares MR, Saleme E, Vargas-Vorackova F, Valdovinos MA. High-resolution esophageal pressure topography (HREPT) in asymptomatic volunteers. A comparative study between solid-state and water-perfused systems. Gastroenterology. 2012;142(Suppl 1):S-239.
3. Jakubowicz M, Wienbeck M, Barnert J. Device dependent problems in esophageal manometry. Dig Dis Sci. 1991;36:25S-28S.
4. Xiang X, Tu L, Zhang X, Xie X, Hou X. Influence of the catheter diameter on the investigation of the esophageal motility through solid-state high-resolution manometry. Dis Esophagus. 2013;26:661-7.
5. Pandolfino JE, Ghosh SK, Zhang Q, Jarosz A, Shah N, Kahrilas PJ. Quantifying EGJ morphology and relaxation with high-resolution manometry: a study of 75 asymptomatic volunteers. Am J Physiol Gastrointest Liver Physiol. 2006;290:G1033-40.
6. Burgos-Santamaría D, Marinero A, Chavarría-Herbozo CM, Teresa Pérez-Fernández T, López-Salazar TR, Santander. Normal values for water-perfused esophageal high-resolution manometry. Rev Esp Enferm Dig. 2015;107:354-8.
7. Wang K, Duan LP, Ge Y, Xia ZW, Xu ZJ. A comparative study of 22-channel water-perfusion system and solid-state system with 36-sensors in esophageal manometery. BMC Gastroenterol. 2012;12:157-60.
8. Kessing BF, Weijenborg PW, Smout AJ, Hillenius S, Bredenoord AJ. Water-perfused esophageal high-resolution manometry: normal values and validation. Am J Physiol Gastrointest Liver Physiol. 2014;306:G491-5.
9. Ghosh SK, Pandolfino JE, Zhang Q, Jarosz A, Shah N, Kahrilas PJ. Quantifying esophageal peristalsis with high resolution manometry: a study of 75 asymptomatic volunteers. Am J Physiol Gastrointest Liver Physiol. 2006;290:G988-97.
10. Kahrilas PJ, Bredenoord AJ, Fox M, Gyawali CP, Roman S, Smout AJPM, Pandolfino JE & International High Resolution Manometry Working Group. The Chicago Classification of esophageal motility disorders, v3.0. Neurogastroenterol Motil. 2015;27:160-74.
11. Nicodème F, Pipa-Muniz M, Khanna K, Kahrilas PJ, Pandolfino JE. Quantifying esophagogastric junction contractility with a novel HRM topographic metric, the EGJ-Contractile Integral: normative values and preliminary evaluation in PPI non-responders. Neurogastroenterol Motil. 2014;26:353-60.
12. Herregods TVK, Roman S, Kahrilas PJ, Smout AJPM, Bredenoord AJ. Normative values in esophageal high-resolution manometry. Neurogastroenterol Motil. 2015; 27:175-87.
13. Capovilla G, Salvador R, Savarino E, Nicoletti L, Zaninotto G, Costantini M. Comparative assessment of tolerability, duration and costs of solid-state vs. water-perfused system for esophageal motility testing – Data from a prospective, randomized, double blind, crossover study. Digestive Disease Week; 03/05/2014; Chicago, 2014.
14. De Schepper HU, Kessing BF, Weijenborg PW, Oors JM, Smout AJ, Bredenoord AJ. Impact of spatial resolution on results of esophageal high-resolution manometry. Neurogastroenterol Motil. 2014;26:922-8.
15. Nicodeme F, Pipa-Muniz M, Khanna K, Kahrilas PJ, Pandolfino JE. Quantifying esophagogastric junction contractility with a novel HRM topographic metric, the EGJ-Contractile Integral: normative values and preliminary evaluation in PPI non-responders. Neurogastroenterol Motil. 2014;26:353-60.
16. Wang D, Xu H, Tang T, Wang J, YU Y, Gyawali CP. Assessment of the esophagogastric junction (EGJ) using the EGJ contractile integral (EGJ-CI) following per-oral endoscopic myotomy (POEM) in achalasia. Rev Esp Enferm Dig. 2018;706-11.
17. Carlson DA, Lin Z, Kahrilas PJ, Sternbach J, Hungness ES, Soper NJ, Balla M, Listernick Z, Tye M, Ritter K, Craft J, Ciolino JD, Pandolfino JE. High-Resolution impedance manometry metrics of the esophagogastric junction for the assessment of treatment response in acalasia. Am J Gastroenterol. 2016;111:1702-10.
18. Da Silva RMB, Herbella FAM, Gualberto D. Normative values for a new water-perfused high resolution manometry system. Arq Gastroenterol. 2018;55(Suppl 1):30-4.
19. Xiang X, Wang A, Tu L, Xie X, Ke M, Yang Y, et al. The differences in the esophageal motility between liquid and solid bolus swallows: A multicenter high-resolution manometry study in Chinese asymptomatic volunteers. Neurogastroenterol Motil. 2019;31:e13574.
20. Srinivas M, Jain M, Bawane P, Jayanthi P. Chicago Classification normative metrics in a healthy Indian cohort for a 16-channel water-perfused high-resolution esophageal manometry system. Neurogastroenterol Motil. 2018;30:e13386.
21. Tseng PH, Wong RKM, Wu JF, Chen CC, Tu CH, Lee YC, et al. Normative values and factors affecting water-perfused esophageal high-resolution impedance manometry for a Chinese population. Neurogastroenterol Motil. 2018;30:e13265.
22. Weijenborg PW, Kessing BF, Smout AJPM, Bredenoord AJ. Normal values for solid-state esophageal high-resolution manometry in a European population; an overview of all current metrics. Neurogastroenterol Motil. 2014;26:654-9.
23. Xiang XL, Wang A, Tu L, Ke MY, Yang YS, Jiang B, et al. The motility of esophageal sphincters during liquid and solid bolus swallows: a multicenter normative value study of high-resolution manometry in China. Neurogastroenterol Motil. 2017;29:e12914.
24. Bogte A, Bredenoord J, Oors J, Siersema PD, Smout AJPM. Normal values for esophageal high-resolution manometry. Neurogastroenterol Motil. 2013 25:762-e579.
25. Kuribayashi S, Iwakiri K, Shinozaki T et. al Clinical impact of different cut-off values in high-resolution manometry systems on diagnosing esophageal motility disorders. J Gastroenterol. 2019;12:1078-82.
26. Sweis R, Anggiansah A, Wong T, Kaufman E, Obrecht S, Fox M. Normative values and inter-observer agreement for liquid and solid bolus swallows in upright and supine positions as assessed by esophageal high-resolution manometry. Neurogastroenterol Motil. 2011;23:509-e198.
27. Hasak S, Brunt LM, Wang D, Gyawali CP. Provocative tests on esophageal high-resolution manometry prior to surgical fundoplication: expanding the manometry protocol. Clin Gastroenterol Hepatol. 2020 Jan 9. pii: S1542-3565(20)30030-6. doi: 10.1016/j.cgh.2020.01.002. [Epub ahead of print].

REVIEW

AG-2019-157
doi.org/10.1590/S0004-2803.202000000-27

Pancreatic steatosis: a new diagnosis and therapeutic challenge in Gastroenterology

Jayanta **PAUL**[1] and Ambalathu Veettil Hussain **SHIHAZ**[2]

Received: 21 October 2019
Accepted: 20 February 2020

ABSTRACT – Fat infiltration in the pancreas is called pancreatic steatosis and it has several synonyms such as pancreatic lipomatosis, non-alcoholic fatty pancreatic disease, lipomatous pseudohypertrophy, fatty replacement, fatty pancreas and fatty infiltration. Pancreatic steatosis describes a disease ranging from infiltration of fat in the pancreas to pancreatic inflammation, and development of pancreatic fibrosis. There are multiple aetiologies of this condition, such as metabolic syndrome, alcohol intake, viral infections, toxins, congenital syndromes, etc. Pancreatic steatosis is usually diagnosed by trans-abdominal ultrasound, computed tomography scan and magnetic resonance imaging. Fatty infiltration in pancreas may lead to pancreatitis, diabetes mellitus and may be a predisposing cause of pancreatic cancer. Now a day, pancreatic steatosis is a common incidental finding during abdominal ultrasonography for other reasons and is a new challenge in Gastroenterology. But there is no guideline for pancreatic steatosis till now. In this review article, we are trying to give an overall idea (aetiologies, diagnosis, management, clinical significances) on pancreatic steatosis.

HEADINGS – Pancreas. Pancreatic diseases. Lipomatosis. Magnetic resonance imaging. Endosonography. Ultrasonography. Review.

INTRODUCTION

Pancreatic steatosis (PS) is the most common benign pathologic condition of the pancreas in adult[1] and commonly related to obesity and associated insulin resistance[2]. PS (used for all forms of pancreatic fat accumulation) has several synonyms such as: pancreatic fatty infiltration (pancreatic fatty infiltration due to obesity, reversed by weight reduction and medications), pancreatic lipomatosis (used for all forms of fatty infiltration of pancreas), fatty replacement (irreversible damage of pancreatic acinar cells and replacement by adipocytes), non-alcoholic fatty pancreatic disease (obesity and metabolic syndrome causing pancreatic fat accumulation), lipomatous pseudohypertrophy (when pancreas is uniformly or focally enlarged and/or the pancreatic exocrine system is altered by fat accumulation, and not related to obesity), fatty pancreas (used for all types of pancreatic fat accumulation)[3,4]. Pancreatic fat accumulation increases with age and replacement of more than 25% of pancreas by fat is associated with severe generalized atherosclerosis and increased risk of development of diabetes mellitus type 2[5]. On abdominal computed tomography scan, pancreas becomes hypodense and on ultrasound (US) examination it shows typical hyperechogenicity. Pancreatic steatosis is the commonly identifying pancreatic pathology during radiological examination but there is no guideline for PS till now. This article is trying to describe pancreatic steatosis in details including aetiology, diagnosis, clinical significance and management.

Definition of pancreatic steatosis

Pancreatic steatosis (PS) is defined by fat accumulation in pancreas and when there is presence of obesity or metabolic syndrome; it is called "non-alcoholic fatty pancreas disease" (NAFPD) and usually associated with NAFLD (non-alcoholic fatty liver disease)[4]. In 1933, Ogilvie first described pancreatic steatosis in literature[4].

Aetiologies of pancreatic steatosis

There are several causes of pancreatic steatosis (FIGURE 1). Similar to NAFLD, advanced age, obesity, metabolic syndrome and insulin resistance are the common risk factors of pancreatic steatosis. Pancreatic fat content is significantly associated with greater body mass index (BMI) and advanced age[6]. Prevalence is extremely low in women with age less than 50 years, but increases

Metabolic causes	Drugs and Toxin	Infection	Others	Local causes
Diabetes	Steroids	Hepatitis B	Haemochromatosis	Chronic pancreatitis
Severe malnutrition	Antiretroviral	AIDS	Cystic fibrosis	Hereditary pancreatitis
Obesity	Rosiglitazone	Reovirus	Old age	Pancreatic ductal obstruction
Dyslipidemia	Gemcitabine		Cirrhosis	
Insulin resistance	Alcohol			
Metabolic syndrome	Octreotide			

FIGURE 1. Aetiologies of pancreatic steatosis.

Declared conflict of interest of all authors: none
Disclosure of funding: no funding received
[1] Desun Hospital and Heart Institute, Department of Gastroenterology, Kolkata, India. [2] University Hospital of North Cumbria, Department of Gastroenterology, UK.
Corresponding author: Jayanta Paul MBBS, MD, DNB (Gastroenterology). E-mail: dr.jayantapaul@gmail.com.

progressively after 50 years of age[7]. Some medications are also responsible for pancreatic steatosis such as steroid hormones[6], antiretroviral therapy[8], rosiglitazone[9], gemcitabine chemotherapy[10] and octreotide[11]. The presence of one or more component of metabolic syndrome, such as diabetes, BMI ≥30, hypertension or hyperlipidemia is associated with 37% increased prevalence of pancreatic steatosis[12]. Chronic alcohol abuse increases pancreatic cholesteryl ester accumulation and induces pancreatic steatosis[13] and usually is seen when person consuming more than 30 gram/day of ethanol[14]. Several infections such as acquired immunodeficiency syndrome (AIDS)[15], chronic hepatitis B[16] and reovirus infection[17] can produce fatty pancreas. Haemochromatosis[4] and malnutrition state such as kwashiorkor[18] can also be responsible NAFPD.

Diagnosis of pancreatic steatosis

Pancreatic steatosis (PS) is most commonly diagnosed by using different imaging techniques[1,3,7] (FIGURE 1). When using any imaging technique to identify pancreatic steatosis, we should know that there is up to 6.2% fatty infiltration of the pancreas in normal individuals. But specificity and sensitivity of different imaging modalities has not been clearly mentioned in several articles on PS.

Ultrasonography in diagnosis of pancreatic steatosis

Ultrasonography (USG) is widely available to detect PS but obesity and bowel gas may cause invisibility of pancreas. To diagnose pancreatic steatosis, pancreas echogenicity is traditionally compared with kidney echogenicity. Hyperechogenic pancreas can be seen in both pancreatic fibrosis and in fatty pancreas. Pancreatic steatosis can be classified into four grades by identifying patterns of pancreas echogenicity in abdominal USG (FIGURE 2); grade 0: when pancreas and renal echogenicity are similar; grade 1: when pancreas echogenicity is increased and is slightly higher than in the kidney; grade 2: when substantial increase in pancreas echogenicity than renal echogenicity but the retroperitoneal fat echogenicity is more than pancreatic echogenicity; and grade 3: the pancreas echogenicity is ≥ retroperitoneal fat echogenicity[19,20].

Computed tomography (CT) in diagnosis of pancreatic steatosis

Focal pancreatic steatosis can be presented as a hypo attenuating mass lesion on CT scan[21]. Non contrast computed tomography (CT) can be used to diagnose PS. Disadvantages of CT scan are exposure to radiation, high cost and can miss focal fatty replacement of pancreas. Fatty pancreas can be classified by CT scan into five grades depending on site of pancreatic involvement (FIGURE 2); Grade 0– normal appearance without fatty replacement, Grade 1– fatty infiltration involving less than 25% of given pancreatic region, Grade 2– fatty replacement that involved 25%–50% of a given pancreatic region, Grade3– fatty replacement involving 50%–75% of a given pancreatic regions; and Grade 4 corresponded to fatty infiltration which involves more than 75% of a given pancreatic region[22]. Fat concentration in pancreas is positively correlated with attenuation indexes in CT scan; this finding suggests that unenhanced CT is useful non-invasive assessment of pancreatic fat[23].

Endoscopic ultrasonography in diagnosis of pancreatic steatosis

Diagnostic accuracy of pancreatic steatosis by endoscopic ultrasound (EUS) is superior to CT scan and magnetic resonance imaging (MRI). The disadvantages are invasive procedure, risk of complications and needs of sedation. EUS is still the most sensitive investigation for pancreas screening but till now pancreatic biopsy is the best method to measure pancreatic fat concentration[24]. However, it is unethical to use EUS as a screening tool[25]. EUS grading system adapted from radiology incorporating the echotexture of the pancreas relative to the spleen as well as the ability to visualize the main pancreatic duct and "salt and pepper" dots in the parenchyma has been suggested to assess fatty pancreas[12].

Magnetic resonance imaging for diagnosis of PS

Magnetic resonance imaging (MRI) can estimate fat concentration in pancreas with high accuracy. MRI may be the test of choice for detection of intrapancreatic fat but available data is little to correlate pancreatic steatosis on MRI or EUS with histology. During MRI, commonly three methods are used to measure the fat in the pancreas. Advanced chemical shift-based gradient echo magnetic resonance imaging technique that measures the proton-density-fat-fraction (PDFF) has been shown to accurately quantify liver fat fraction when compared with the magnetic resonance spectroscopy (MRS) technique[26] and reliably measures pancreatic fat content when compared with other MRI imaging techniques[27].

Pathological classification

Pathologically pancreatic steatosis is classified into homogenous pancreatic lipomatosis and non homogenous pancreatic lipomatosis. Again non homogenous lipomatosis is classified into four types; type 1a: head is usually replaced by fat, type 1b: head, neck and body are replaced by fat, type 2a: head and uncinate process replaced by fat, type 2b: most of the pancreas except the peribiliary region is replaced by fat[28]. However, histological examination is not recommended for only diagnosis of pancreatic steatosis.

Clinical significances

Development of diabetes mellitus: Wang et al. (2014) in their study found that the patients with fatty pancreas has an higher risk of development of diabetes than patients without fatty pancreas[29]

Grading of Pancreatic steatosis	USG Findings	CT findings
Grade 0	When pancreas and renal echogenicity are similar	Normal appearance without fatty replacement
Grade 1	When pancreas echogenicity was slightly higher than in the kidney	Fatty infiltration involving less than 25% of given pancreatic region
Grade 2	When substantial increase in pancreas echogenicity than renal echogenicity but lower than the retroperitoneal fat echogenicity	Fatty replacement that involved 25%–50% of a given pancreatic region
Grade 3	The pancreas echogenicity is similar to or higher than the retroperitoneal fat	Fatty replacement involving 50%–70% of a given pancreatic regions
Grade 4		Fatty infiltration which involves more than 75% of a given pancreatic region

FIGURE 2. Pancreatic steatosis grading by trans abdominal ultrasonography (UGS) and abdominal computed tomography (CT).

and newly diagnosed patients with type 2 diabetes mellitus (DM2) have significantly greater pancreatic fat content[30]. Pancreatic islets cell fat infiltration leads to a reduced insulin secretion and increases development of DM2[31]. Presence of >25% pancreatic fatty infiltration is associated with significantly increased risk of development of type 2 diabetes mellitus and generalized atherosclerosis[32].

Post operative pancreatic fistula: developing a pancreatic fistula is significantly increased after pancreatic surgery in patients with pancreatic steatosis[33,34], and have a ten times higher risk of incidence of fistula formation in pancreas than those with fibrotic pancreas[35].

Carotid atherosclerosis: pancreatic steatosis is an independent risk factor for the development of carotid atherosclerosis in non-obese subjects with type 2 diabetes mellitus. So, it could be a marker of higher risk of cardiovascular disease, especially in non-obese individuals[36].

Pancreatitis: risk factors of pancreatic steatosis such as obesity and components of metabolic syndrome are known risk factors for acute pancreatitis. When acute pancreatitis due to any aetiology affects fatty pancreas, it is usually severe in intensity[37] and also is a significant risk factor for developing subclinical chronic pancreatitis[38].

Pancreatic carcinoma: fatty pancreas is independently associated with an increased risk of development of pancreatic carcinoma[3,39]. PS promotes dissemination and lethality of pancreatic carcinoma by alteration of tumour microenvironment, enhanced tumour spread[40]. Patients with increased pancreatic fat have a poor outcome than those who develop cancer in a pancreas without steatosis. Chronic inflammation with excessive fat accumulation might be the cause of cell injury and development of pancreatic carcinoma[41]. But another study found that there is no association between fatty pancreas and chronic pancreatitis or carcinoma of pancreas[12]. Non alcoholic fatty liver disease (NAFLD) is positively correlated with pancreatic cancer in these patients and NAFLD patients with pancreatic cancer have poorer outcome than patients without NAFLD[42]. Pathophysiology of development of pancreatic cancer in NAFPD is similar to how NAFLD causes liver cancer [4].

Pancreatic exocrine insufficiency: pancreatic steatosis can lead to exocrine pancreatic insufficiency (EPI) by (1) fat droplet accumulation in pancreatic acinar cells and consequent lipotoxicity, (2) destruction of acinar cells by both inflammation and fatty replacement, (3) by negative paracrine effect of adipocytes. Exocrine function in NAFPD patients has never been extensively investigated. In few case reports, patients with weight loss and massive steatorrhea were found to have severe pancreatic steatosis diagnosed by abdominal computed tomograms (CT scan) in whom the administration of pancreatic extracts improved symptoms[43,44].

Cardiovascular risk: risk factors of fatty pancreas are also risk factors of cardiovascular accident. The presence of NAFPD on ultrasonography is associated with increased aortic intima media thickness and epicardial adipose tissue[45]. Therefore, it could be a marker of a higher risk of cardiovascular disease.

Pancreatic enzymes level in PS: few study[46] showed that serum amylase value is significantly lower in patients with fatty pancreas compared to normal pancreas individuals but another study indicates that there is no association between fatty pancreas and serum amylase or lipase concentrations[12]. Benign pancreatic hyperenzymemia (BPH) or Gullo's syndrome is a diagnosis of exclusion and diagnosed by persistently elevated pancreatic enzymes without any clinical or pathological evidence of pancreatic disease. There is no relationship between NAFPD and Gullo's syndrome.

Correlation between non-alcoholic fatty liver and non-alcoholic fatty pancreas

Pancreatic steatosis is common in patients with NAFLD, and pancreatic fat content positively correlates with liver steatosis grading determined by histology[46,47]. Patients with histology-determined liver fibrosis have significantly less pancreatic fat infiltration than those without evidence of liver fibrosis[48]. Fatty infiltration in pancreas causes β-cell dysfunction, which may also lead to hepatic steatosis[49] and pancreatic fat also may play a role in the development of non alcoholic steatohepatitis (NASH)[37].

Differential diagnosis

Pancreatic steatosis of the dorsal caudal pancreas must be distinguished from dorsal pancreatic agenesis. Lipomatous pseudohypertrophy of the pancreas has probably been considered as a differential diagnosis of pancreatic steatosis[50,51].

Management of pancreatic steatosis (FIGURE 3)

There is no specific treatment for fatty pancreas. Until now

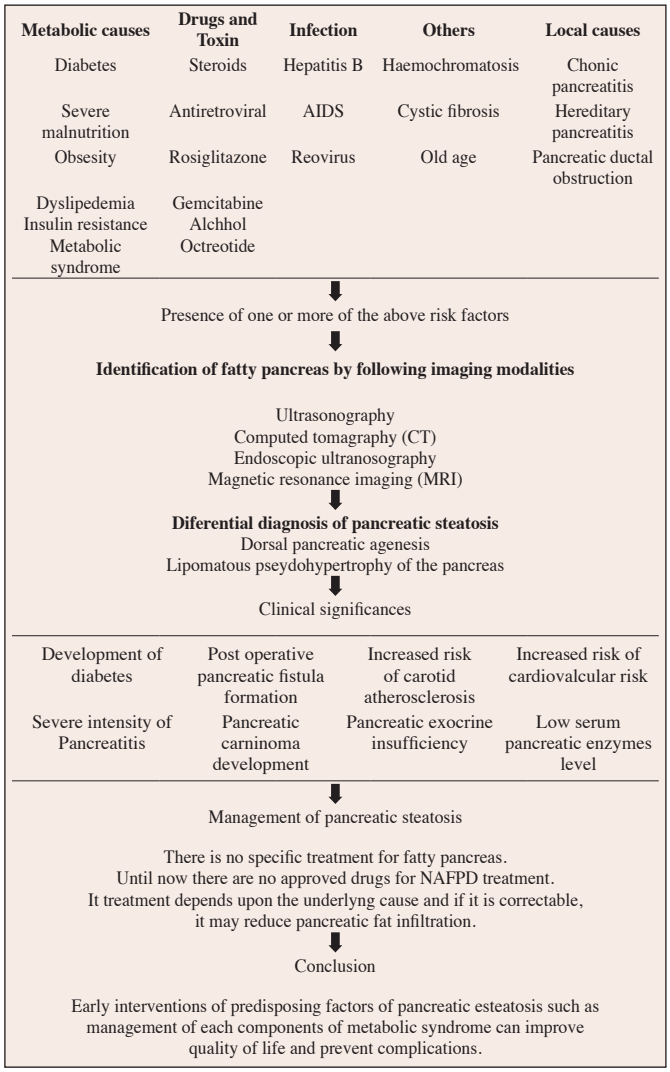


FIGURE 3. Flow chart of a practical approach of pancreatic steatosis (aetiology, diagnosis, clinical significance and management).

there are no approved drugs for NAFPD treatment. Treatment of PS depends on the underlying cause and if it is correctable, it may reduce pancreatic fat infiltration. If patient is having metabolic syndrome then tight diabetes control, diet restriction, physical exercise and weight reduction may improve condition. Pancreatic steatosis can be treated with a healthy diet, exercise, less meat consumption, and smoking cessation[52].

CONCLUSION

In majority cases, pancreatic steatosis is an incidental finding during trans-abdominal ultrasonography. It is commonly associated with metabolic syndrome, alcohol abuse and patients with non alcoholic fatty liver disease. NAFPD is usually diagnosed by radiological investigations such as abdominal USG, abdominal CT scan or abdominal MRI. Fatty pancreas has an increased risk of development of diabetes, pancreatic fistula after pancreatic surgery, development of carotid atherosclerosis in non-obese individuals, risk of development of pancreatic carcinoma, developing subclinical chronic pancreatitis and exocrine pancreatic insufficiency. Therefore early diagnosis and interventions for predisposing factors of pancreatic steatosis such as each component of metabolic syndrome can improve quality of life and prevent complications. But Until now there are no approved specific drugs for NAFPD treatment.

Authors' contribution

Paul J: conceptualization, methodology, supervision, writing-original draft, writing-review & editing. Shihaz AVH: conceptualization, writing-review & editing.

Orcid

Jayanta Paul: 0000-0003-1188-1766.
Ambalathu Veettil Hussain Shihaz: 0000-0001-5581-8166.

Paul J, Shihaz AVH. Esteatose pancreática: um novo diagnóstico e desafio terapêutico na Gastroenterologia. Arq Gastroenterol. 2020;57(2):216-20.

RESUMO – A infiltração de gordura no pâncreas é chamada de esteatose pancreática ou lipomatose pancreática e tem vários sinônimos tais como: doença pancreática gordurosa não alcoólica, pseudo hipertrofia lipomatosa, reposição gordurosa, pâncreas gorduroso e infiltração gordurosa. A esteatose pancreática descreve uma doença que vai desde a infiltração de gordura no pâncreas até a inflamação pancreática com o desenvolvimento de fibrose pancreática. Existem múltiplas causas dessa condição, como síndrome metabólica, ingestão de álcool, infecções virais, toxinas, síndromes congênitas, etc. A esteatose pancreática é geralmente diagnosticada por ultrassom trans-abdominal, tomografia computadorizada ou ressonância magnética. A infiltração gordurosa no pâncreas pode levar à pancreatite e pode ser uma causa predisponente ao câncer de pâncreas. Hoje em dia, a fibrose pancreática é um achado incidental comum durante a ultrassonografia abdominal realizada por outras razões e é um novo desafio na Gastroenterologia. Mas não há diretriz para esteatose pancreática até agora. Neste artigo de revisão, objetivamos dar uma ideia geral sobre esteatose pancreática.

DESCRITORES – Pâncreas. Pancreatopatias. Lipomatose. Imagem por ressonância magnética. Endossonografia. Ultrassonografia. Revisão.

REFERENCES

1. Ozbulbul, NI, Yurdakul, M, Tola, M. Does the visceral fat tissue show better correlation with the fatty replacement of the pancreas than with BMI? Eurasian J Med. 2010;42:24-7.
2. van Geenen EJ, Smits MM, Schreuder TC, van der Peet DL, Bloemena E, Mulder CJ. Nonalcoholic fatty liver disease is related to nonalcoholic fatty pancreas disease. Pancreas. 2010;39:1185-90.
3. Pezzilli R, Calculli L. Pancreatic steatosis: Is it related to either obesity or diabetes mellitus? World J Diabetes. 2014;5:415-9.
4. Smits MM, van Geenen EJ. The clinical significance of pancreatic steatosis. Nat Rev Gastroenterol Hepatol. 2011;8:169-77.
5. Stamm BH. Incidence and diagnostic significance of minor pathologic changes in the adult pancreas at autopsy: a systematic study of 112 autopsies in patients without known pancreatic disease. Hum Pathol. 1984;15:677-83.
6. Rosso E, Casnedi S, Pessaux P, Casnedi S, Pessaux P, Oussoultzoglou E, Panaro F, Mahfud M, et al. The role of "fatty pancreas" and of BMI in the occurrence of pancreatic fistula after pancreaticoduodenectomy. J Gastrointest Surg. 2009;13: 1845-51.
7. Wong VW, Wong GL, Yeung DK, et al. Fatty pancreas, insulin resistance, and β-cell function: a population study using fat-water magnetic resonance imaging. Am J Gastroenterol. 2014;109:589-97.
8. Villarroya F, Domingo P, Giralt M. Drug-induced lipotoxicity: lipodystrophy associated with HIV-1 infection and antiretroviral treatment. Biochim Biophys Acta. 2010;1801:392-9.
9. Fernandes-Santos C, Evangelista Carneiro R, de Souza Mendonca L, Barbosa Aguila M, Mandarim-de-Lacerda CA. Rosiglitazone aggravates nonalcoholic fatty pancreatic disease in C57BL/6 mice fed high-fat and high-sucrose diet. Pancreas. 2009;38:e80-e86.
10. Makay O, Kazimi M, Aydin U, Nart D, Yilmaz F, Zeytunlu M, et al. Fat replacement of the malignant pancreatic tissue after neoadjuvant therapy. Int J Clin Oncol. 2010;15:88-92.
11. Yu T, Liu R, Li M, Li X, Qiang O, Huang W, Tang C. Effects of octreotide on fatty infiltration of the pancreas in high-fat diet induced obesity rats. Wei Sheng Yan Jiu. 2014;43:186-92.
12. Sepe PS, Ohri A, Sanaka S, Berzin TM, Sekhon S, Bennett G, et al. A prospective evaluation of fatty pancreas by using EUS. Gastrointest Endosc. 2011;73: 987-93.
13. Wilson JS, Colley PW, Sosula L, Pirola RC, Chapman BA, Somer JB. Alcohol causes a fatty pancreas. A rat model of ethanol-induced pancreatic steatosis. Alcohol Clin Exp Res. 1982;6:117-21.
14. Noronha M, Salgadinho A, Ferreira De Almeida MJ, Dreiling DA, Bordalo O. Alcohol and the pancreas. I. Clinical associations and histopathology of minimal pancreatic inflammation. Am J Gastroenterol. 1981;76:114-9.
15. Oliveira NM, Ferreira FA, Yonamine RY, Chehter EZ. Antiretroviral drugs and acute pancreatitis in HIV/AIDS patients: is there any association? A literature review. Einstein (Sao Paulo). 2014;12:112-9.
16. Sasaki M, Nakanuma Y, Ando H. Lipomatous pseudohypertrophy of the pancreas in a patient with cirrhosis due to chronic hepatitis B. Pathol Int. 1998;48: 566-8.
17. Walters MN, Leak PJ, Joske RA, Stanley NF, Perret DH. Murine infection with reovirus 3. pathology of infection with types 1 and 2. Br J Exp Pathol. 1965;46:200-12.
18. Diamond I, Vallbona C. Kwashiorkor in a North American white male. Pediatrics. 1960;25:248-57.
19. Lee JS, Kim SH, Jun DW, Han JH, Jang EC, Park JY, et al. Clinical implications of fatty pancreas: correlations between fatty pancreas and metabolic syndrome. World J Gastroenterol. 2009;15:1869-75.
20. Marks WM, Filly RA, Callen PW. Ultrasonic evaluation of normal pancreatic echogenicity and its relationship to fat deposition. Radiology. 1980;137:475-9.
21. Hague J, Amin Z. Focal pancreatic lesion: can a neoplasm be confidently excluded? Br J Radiol. 2006;79:627-9.
22. Soyer P, Spelle L, Pelage JP, Dufresne AC, Rondeau Y, Gouhiri M, et al. Cystic fibrosis in adolescent and adults: Fatty replacements of the pancreas CT evaluation and functional correlation. Radiology. 1999;210:611-5.
23. Kim SY, Kim H, Cho JY, Lim S, Cha K, Lee KH, et al. Quantitative assessment of pancreatic fat by using unenhanced CT: pathologic correlation and clinical implications. Radiology. 2014;271:104-12.

24. Lesmana CRA, Ho KY, Lesmana LA. Impact of endoscopic ultrasound procedures in various pancreatobiliary disorders in Indonesia based on a case series in a private hospital. Case Rep. Gastroenterol. 2015;9:206-14.
25. Larghia A, Petroneb MC, Galassoa D, Arcidiacono PG. Endoscopic ultrasound in the evaluation of pancreatobiliary disorders. Dig Liver Dis. 2010;42:6-15.
26. Kang GH, Cruite I, Shiehmorteza M, Wolfson T, Gamst AC, Hamilton G, et al. Reproducibility of MRI determined proton density fat fraction across two different MR scanner platforms. J Magn Reson Imaging. 2011;34:928-34.
27. Schwenzer NF, Machann J, Martirosian P, Stefan N, Schraml C, Fritsche A, et al. Quantification of pancreatic lipomatosis and liver steatosis by MRI: comparison of in/opposed-phase and spectral-spatial excitation techniques. Invest Radiol. 2008;43:330-7.
28. Mortelé KJ, Rocha TC, Streeter JL, Taylor AJ. Multimodality imaging of pancreatic and biliary congenital anomalies. Radiographics. 2006;26:715-31.
29. Wang CY, Ou HY, Chen MF, Chang TC, Chang CJ. Enigmatic ectopic fat: prevalence of non-alcoholic fatty pancreas disease and its associated factors in a Chinese population. J Am Heart Assoc. 2014;3:e000297.
30. Chai J, Liu P, Jin E, Su T, Zhang J, Shi K, et al. MRI chemical shift imaging of the fat content of the pancreas and liver of patients with type 2 diabetes mellitus. Exp Ther Med. 2016;11:476-80.
31. Lameloise N, Muzzin P, Prentki M, Assimacopoulos-Jeannet F. Uncoupling protein 2: a possible link between fatty acid excess and impaired glucose-induced insulin secretion? Diabetes. 2001;50:803-9.
32. Stamm BH. Incidence and diagnostic significance of minor pathologic changes in the adult pancreas at autopsy: a systematic study of 112 autopsies in patients without known pancreatic disease. Hum Pathol. 1984;15:677-83.
33. Mathur A, Marine M, Lu D, Swartz-Basile DA, Saxena R, Zyromski NJ, Pitt HA. Nonalcoholic fatty pancreas disease. HPB (Oxford) 2007;9:312-8.
34. Tranchart H, Gaujoux S, Rebours V, Vullierme MP, Dokmak S, Levy P, et al. Preoperative CT scan helps to predict the occurrence of severe pancreatic fistula after pancreaticoduodenectomy. Ann Surg. 2012;256:139-45.
35. Patel AC, Yagnik VD. Evaluation of risk factors for postoperative pancreatic fistula following pancreaticoduodenectomy. Formos J Surg. 2019;52:76-83.
36. Kim MK, Chun HJ, Park JH, Yeo DM, Baek KH, Song KH, et al. The association between ectopic fat in the pancreas and subclinical atherosclerosis in type 2 diabetes. Diabetes Res Clin Pract. 2014;106:590-6.
37. Van Geenen EJ, Smits MM, Schreuder TC, van der Peet DL, Bloemena E, Mulder CJ. Nonalcoholic fatty liver disease is related to nonalcoholic fatty pancreas disease. Pancreas. 2010;39:1185-90.
38. Fujii M, Ohno Y, Yamada M, Kamada Y, Miyoshi E. Impact of fatty pancreas and lifestyle on the development of subclinical chronic pancreatitis in healthy people undergoing a medical check up. Environ Health Prev Med. 2019; 24:10.
39. Hori M, Takahashi M, Hiraoka N, Yamaji T, Mutoh M, Ishigamori R, et al. Association of pancreatic Fatty infiltration with pancreatic ductal adenocarcinoma. Clin Transl Gastroenterol. 2014;5:e53.
40. Mathur A, Hernandez J, Shaheen F, Shroff M, Dahal S, Morton C, et al. Preoperative computed tomography measurements of pancreatic steatosis and visceral fat: prognostic markers for dissemination and lethality of pancreatic adenocarcinoma. HPB (Oxford). 2011;13:404-10.
41. Jeannet FA. Fat storage in pancreas and in insulin-sensitive tissues in pathogenesis of type 2 diabetes. Int. J. Obes. 2004;28:53-57.
42. Chang CF, Tseng YC, Huang HH, Shih YL, Hsieh TY, Lin HH. Exploring the relationship between nonalcoholic fatty liver disease and pancreatic cancer by computed tomographic survey. Intern Emerg Med. 2018;13:191-7.
43. Lozano M, Navarro S, Perez-Ayuso R, Llach J, Ayuso C, Guevara MC, Ros E. Lipomatosis of the pancreas: an unusual cause of massive steatorrhea. Pancreas. 1988;3:580-2.
44. Aubert A, Gornet JM, Hammel P, Lévy P, O'Toole D, Ruszniewski P, et al. Diffuse primary fat replacement of the pancreas: an unusual cause of steatorrhea. Gastroenterol Clin Biol. 2007;31:303-6.
45. Selim Kul S, Ayşegül Karadeniz A, Dursun I, Şahin S, Faruk Çırakoğlu Ö, Raşit Sayın M, et al. Non-Alcoholic Fatty Pancreas Disease is Associated with Increased Epicardial Adipose Tissue and Aortic Intima-Media Thickness. Acta Cardiol Sin. 2019;35:118-25.
46. Wu WC, Wang CY. Association between non-alcoholic fatty pancreatic disease (NAFPD) and the metabolic syndrome: casecontrol retrospective study. Cardiovasc Diabetol 2013;12:77.
47. Nacif LS, Rocha-Santos V, Claro LCL, Vintimilla A, Ferreira LA, Arantes RM, et al. Liver biopsy may facilitate pancreatic graft evaluation: Positive association between liver steatosis and pancreatic graft adipose infiltration. Clinics (Sao Paulo). 2018; 73:e49.
48. Patel NS, Peterson MR, Brenner DA, Heba E, Sirlin C, Loomba R. Association between novel MRI-estimated pancreatic fat and liver histology-determined steatosis and fibrosis in non-alcoholic fatty liver disease. Aliment Pharmacol Ther. 2013;37:630-9.
49. Hannukainen JC, Borra R, Linderborg K, Kallio H, Kiss J, Lepomäki V, et al. Liver and pancreatic fat content and metabolism in healthy monozygotic twins with discordant physical activity. J Hepatol. 2011;54:545-52.
50. Yasuda M, Niina Y, Uchida M, Fujimori N, Nakamura T, Oono T, et al. A case of lipomatous pseudohypertrophy of the pancreas diagnosed by typical imaging. JOP. 2010;11:385-8.
51. Shimada M, Shibahara K, Kitamura H, Demura Y, Hada M, Takehara A, et al. Lipomatous pseudohypertrophy of the pancreas taking the form of huge massive lesion of the pancreatic head. Case Rep Gastroenterol. 2010;4:457-6.
52. Ramkissoon R, Gardner TB. Pancreatic Steatosis: An Emerging Clinical Entity. Am J Gastroenterol. 2019;114:1726-34.

AG-2020-07
doi.org/10.1590/S0004-2803.202000000-35

Robotic redo pancreaticojejunostomy for stenosis following pancreaticoduodenectomy: an alternative technique

Marcel Autran C **MACHADO**, Fábio F **MAKDISSI**, Marcel C C **MACHADO** and José Celso **ARDENGH**

Received: 23 January 2020
Accepted: 7 February 2020

Pancreaticoduodenectomy is the procedure of choice for several diseases from benign or pre-malignant lesions to malignancy[1]. One of the most frequent late complications is the stenosis of the pancreato-enteric anastomosis[2-4]. This complication is observed in 25%–60% of radiological images during follow-up[2]. Although frequent, this stenosis is often asymptomatic but in certain circumstances this stenosis may lead to recurrent acute pancreatitis, pain and pancreatic exocrine insufficiency. About 2% of all patients will develop a symptomatic pancreaticojejunostomy stricture needing treatment[3,4]. We present an alternative technique for the surgical revision of pancreaticojejunostomy using robotic approach. A 60-year-old woman underwent laparoscopic Whipple procedure two years ago. After 6 months, she presented with acute pancreatitis. MRI showed mild dilation of the main pancreatic duct and the patient was conservatively treated. However, since then, she presented several episodes of acute pancreatitis. MRI showed a complete stenosis of the pancreaticojejunostomy with pronounced dilation of the main pancreatic duct (FIGURE 1). Multidisciplinary team decided for revision surgery (E-VIDEO*). Robotic redo pancreaticojejunostomy was indicated (FIGURE 2). A new technique was used (E-VIDEO*). After adhesiolysis, the pancreato-enteric anastomosis is identified (FIGURES 3.A and 3.B). Distal pancreas is then detached from the jejunal loop with scissors from anterior towards posterior interrupted sutures. The duct-to-mucosa anastomosis area, which is stenotic is divided with scissors. However, it is completely fibrotic, and the previous anastomosis cannot be identified. The posterior layer is kept intact. Next step is to remove a part of the proximal pancreas in a pyramidal shape towards the posterior layer. This maneuver removes the fibrotic area and the dilated pancreatic duct is opened (FIGURES 3.C and 3.D). A small opening in the jejunum is performed and a duct-to-mucosa anastomosis is performed using absorbable continuous suture (FIGURES 4.A and 4.B). Anastomosis is completed with interrupted seromuscular-pancreatic sutures (FIGURES 4.C and 4.D). Operation is completed with drainage of the abdominal

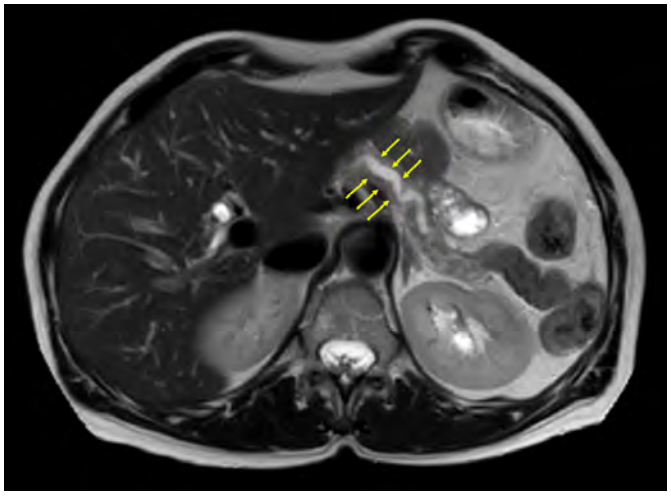


FIGURE 1. Preoperative MRI shows stenosis of the pancreato-jejunostomy with marked dilation of the distal main pancreatic duct.

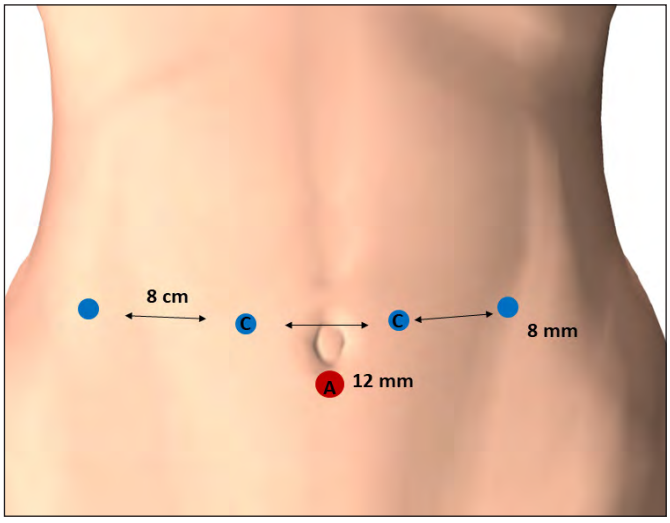


FIGURE 2. Schematic drawing shows type and position of trocars used. The camera (C) is used in two different positions. A. auxiliary port used by bedside surgeon (red dot). A minimum 8 cm distance should be kept between robotic arms (blue dot).

Declared conflict of interest of all authors: none
Disclosure of funding: no funding received
Nove de Julho Hospital, São Paulo, SP, Brasil.
Corresponding author: Marcel Autran C. Machado, M.D. E-mail: dr@drmarcel.com.br
*** Video: https://www.youtube.com/watch?v=WOEOgyYl_xk**

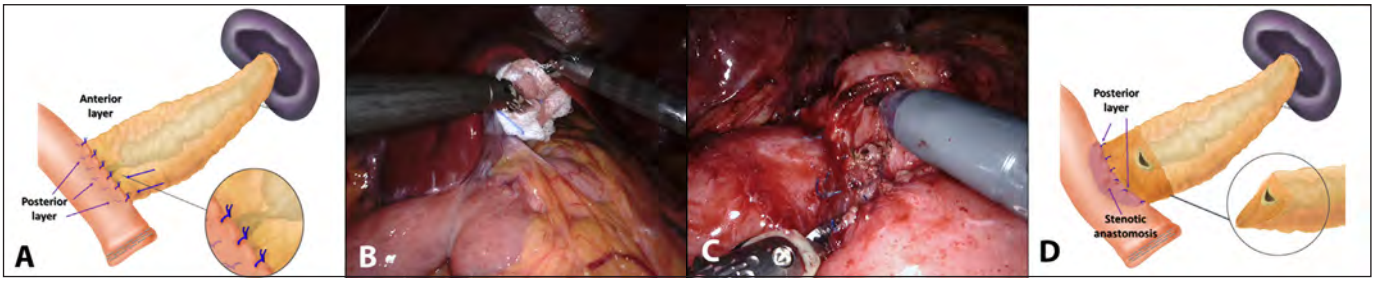


FIGURE 3. Alternative technique for redo pancreaticojejunostomy.
A. Schematic drawing shows pancreaticojejunostomy with stenosis of duct-to-mucosa anastomosis. Close-up shows the site of stenosis. **B.** Intraoperative view after adhesiolysis. Pancreaticojejunostomy is identified. **C.** Intraoperative view after removal of the anterior layer and pyramidal resection of the pancreas exposing the dilated main pancreatic duct. Posterior layer is preserved to maintain the anastomosis assembled. **D.** Schematic drawing after removal of the anterior layer and partial pancreatic resection shows dilated main pancreatic duct, stenotic duct-to-mucosa anastomosis and preserved posterior layer. Close-up shows the pyramidal resection of pancreas, preserving posterior layer.

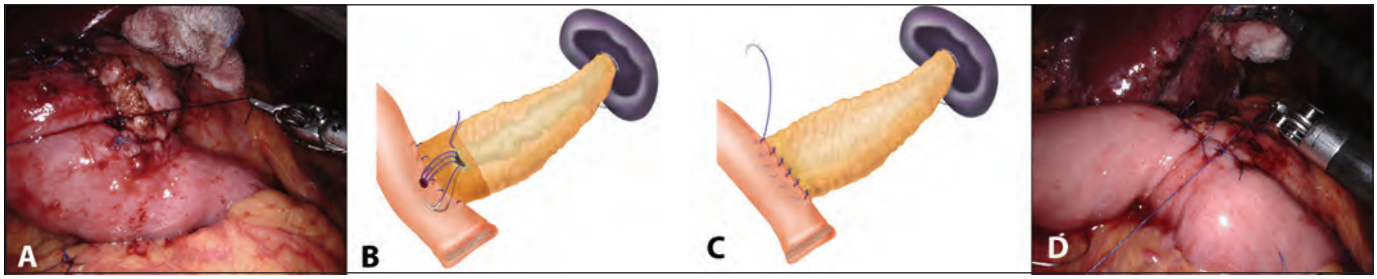


FIGURE 4. Alternative technique for redo pancreaticojejunostomy.
A. Intraoperative view after completion of duct-to-mucosa anastomosis. **B.** Schematic drawing shows duct-to-mucosa anastomosis. **C.** Schematic drawing after completion of redo pancreaticojejunostomy. **D.** Intraoperative view after completion of redo pancreaticojejunostomy.

cavity. Operative time for docking of the robotic system was four minutes. Redo pancreaticojejunostomy took one hour. Estimated blood loss was minimum, and recovery was uneventful. Patient was discharged on the 3rd postoperative day. No pancreatic fistula was observed, and drain was removed on the 5th postoperative day. Patient presented no recurrence of acute pancreatitis during one year of follow-up. Robotic redo pancreaticojejunostomy is feasible and safe. This alternative technique maintains this anastomosis assembled thus reducing the operative time and technical difficulties to perform this complex operation. This video shows the different steps necessary to perform this operation and will be useful for all surgeons having to perform a revision pancreaticojejunostomy.

Authors' contribuition

Machado MAC and Makdissi FF carried out the operative procedure. Machado MCC and Machado MAC conceived the technique. Ardengh JC and Makdissi FF supervised and commented on the manuscript. All authors discussed the results and contributed to the final manuscript.

Orcid

Marcel Autran C Machado: 0000-0002-4981-7607.
Fábio Ferrari Makdissi: 0000-0001-8202-5890.
Marcel C C Machado: 0000-0002-0729-1635
José Celso Ardengh: 0000-0002-5932-2499.

Machado MAC, Makdissi FF, Machado MCC, Ardengh JC. Pancreatojejunostomia revisional via robótica. Alternativa técnica no tratamento de estenose após duodenopancreatectomia. Arq Gastroenterol. 2020;57(2):221-2.

REFERENCES

1. Machado MA, Surjan R, Bassères T, Ardengh A, Makdissi F. Robotic pancreaticoduodenectomy after Roux-en-Y gastric bypass - Video article. Surg Oncol. 2019;29:118-9.
2. Sho M, Nakajima Y, Kanehiro H, Hisanaga M, Nishio K, Nagao M et al. A new evaluation of pancreatic function after pancreatoduodenectomy using secretin magnetic resonance cholangiopancreatography. Am J Surg. 1998;176:279-82.
3. Sledzianowski JF, Muscari F, Suc B, Fourtanier G. Recurrent pancreatitis after pancreaticoduodenectomy: reoperation for stenosis of the pancreaticojejunostomy. Ann Chir. 2004;129:37-40.
4. Mucci-Hennekinne S, Brachet D, Clouston H, Pessaux P, Hamy A, Arnaud JP. Management of a stenotic pancreatico-digestive tract anastomosis following pancreatoduodenectomy. J Hepatobiliary Pancreat Surg. 2007;14:514-7.

ERRATUM

doi.org/10.1590/S0004-2803.202000000-42

In article **Normal values of esophageal high-resolution manometry: a Brazilian multicenter study**, DOI: 10.1590/S0004-2803.202000000- 40, published in journal **Arq Gastroenterol. 2020;57(2):209-15, in page 209:**

Which was read

Results: The mean age was 40.5±13.2 years. Our normative metrics were integrated relaxation pressure <16 mmHg and distal contractile integral (708-4111 mmHg.cm.s) distal latency was <6 s and peristaltic break size (>4 cm). For EGJ-CI the range 5th-95th was 21.7-86.9 mmHg.cm.s.

Read

Results: The mean age was 40.5±13.2 years. Our normative metrics were integrated relaxation pressure <16 mmHg and distal contractile integral (708-4111 mmHg.cm.s) distal latency was <6 s and peristaltic break size (<4.0 cm). For EGJ-CI the range 5th-95th was 21.7-86.9 mmHg.cm.s.

And page 213:

Which was read

Peristaltic break size: >4.0 cm

Read

Peristaltic break size: <4.0 cm

PATROCÍNIO

IBEPEGE
Instituto Brasileiro de Estudos e Pesquisas de Gastroenterologia e Outras Especialidades

HOSPITAL IGESP