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The prevalence of self-reported gluten sensitivity (SRGS) in irritable bowel syndrome (IBS)in a Brazilian community. A pilot study

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ABSTRACT

Background – A significant number of irritable bowel syndrome (IBS) patients report onset of symptoms after ingestion of a specific food, including those containing gluten. NCGS includes both intestinal and extra-intestinal symptoms which are related to the ingestion of gluten containing food-after exclusion of celiac disease (CD) and wheat allergy. The overlap between irritable bowel syndrome (IBS) and NCGS has been described but the knowledge of the etiopathogenesis of this clinical entity is incomplete. In Brazil, data on the prevalence of IBS and its association with food intolerance are scarce. Objective – To study the prevalence of SRGS in a group of volunteers diagnosed with IBS in a Brazilian community. Methods – A total of 400 volunteers over 18 years old were selected from students and staff of the Medical School of the Fluminense Federal University, Brazil. Participants completed a questionnaire divided in basic demographic information (age, sex), evaluation of IBS diagnosis in accordance with the Rome III criteria and self-reported food intolerance, including gluten. Results – Eighty-seven (21.7%) (Group I) [mean age 30.4±12.65 (77.4%) females] fulfilling the Rome III criteria for IBS. Twenty-six (32%) reported gastrointestinal symptoms after ingestion of food in general and 28 (32.1%) after gluten ingestion. Within the 313 volunteers non-IBS (78.2%) (Group II) [mean age 30.6±21.77, 215 (68.2%) females] 66 (21%) and 50 (15.9%) reported gastrointestinal symptoms after ingestion of food in general and gluten respectively. Demographic data (mean age and

sex) were not statistically different when we compared the two groups of volunteers ($p>0.05$). Conclusion – The report of gastrointestinal symptoms after ingestion of food in general and gluten-containing foods were statistically different in the two groups ($p<0.05$). The interaction between IBS, food intolerance and NCGS needs to be better defined, since the role of diet in IBS and its feeding management is an essential condition for the treatment of most of those patients

Keywords: IBS; NCGS; SRGS; prevalence; Brazilian community.

1 INTRODUCTION

Irritable bowel syndrome (IBS) is one of the most common gastrointestinal diseases, with an estimated overall prevalence of 10% to 20% [1-5]. Characterized by recurrentsymptoms and multifactorial etiopathogenesis, IBS has no biological markers available for its diagnosis [1-5]. Given the complexity of its pathophysiology and the clinical subgroups resulting from this set of options, IBS is clinically defined as a biopsychosocial disease [7,8].

A significant number of IBS patients have reported that their symptoms are triggered by at least one food item [9-12]. Several food groups, such as fermentable oligosaccharides, disaccharides, monosaccharides, polyols and gluten/wheat, have been recognized as possible triggers of symptoms compatible with IBS diagnosis [12-19] and a subset of IBS patients report worsening symptoms when they consume gluten-containing foods [16-21].

This association is included in the concept of IBS type disorders [22]. One of the IBS-like disorders was defined as non-celiac gluten sensitivity (NCGS). NCGS includes both intestinal and extra-intestinal symptoms which are related to the ingestion of gluten-containing food after exclusion of celiac disease (CD) and wheat allergy [22-25]. This association between gluten intake and the occurrence of symptoms in the absence of CD and wheat allergy was first described in the late 1970s by Cooper and Ellis and recently defined by the Salerno criteria [26,27].NCGS is a new clinical entity without a specific clinical outline and the NCGS nomenclature is often used in the media and at the professional level, piquing the interest of the scientific community and the general population. Some authors report that NCGS was described in 6% of the population. Increased global wheat consumption in recent decades and higher gluten concentration in the various forms of wheat foods available for daily consumption could be associated with this high prevalence [22,27,28].

However, many questions related to this clinical entity remain unanswered. The true prevalence of NCGS, diagnostic criteria or biomarkers, the specific wheat ingredient that triggers the symptoms, and the immunopathological process associated with the symptoms are not yet identified. In addition, the high frequency of self-diagnosis, stimulated by the media, has been a barrier to the proper evaluation of patients [22,27-38].

Overlapping IBS with NCGS has also raised many questions, mainly because it may influence the therapeutic treatment of IBS patients who report food intolerance and the onset of IBS-compatible

symptoms after ingestion of gluten-containing foods that improve with their withdrawal [39-42]. However, most of these patients report intolerance and worsening of symptoms with other nutrients in their diet [32-34]. So, after a detailed clinical evaluation, the symptoms associated with IBS can be triggered by fermentable oligo-, di-, monosaccharides and polyols (FODMAPs) and not by the gluten. These findings suggest that patients with IBS symptoms have difficulties with foods in general. It is very probable that IBS causes food intolerance and not the opposite [37-40]. More careful planning of clinical trials will lead to a better understanding of the nature of NCGS and its association with IBS [42-44]. The objective of this research was to study the prevalence of SRGS in a group of volunteers diagnosed with IBS in a Brazilian community.

2 METHODS

Study design – a cross-sectional study A total of 400 volunteers were evaluated between September 2017 and January 2018. They were selected between students and employees of the Medical School of the Fluminense Federal University, Niterói, RJ, Brazil, recruited through a poster affixed on the door of the group of study of intestinal diseases (outpatient unit), Antonio Pedro University Hospital in order to obtain a sample that would not comprehend ambulatory or hospital patients, but the population in general. Niterói is located in the metropolitan region of Rio de Janeiro, is considered an urban area and has a population of about 600,000 inhabitants.

The volunteers were first evaluated in outpatient clinics for functional gastrointestinal diseases at Antonio Pedro University Hospital. After agreeing to participate in the study volunteers completed a questionnaire divided in three sections: 1- basic demographic information (age, sex), 2- evaluation of IBS diagnosis in accordance with the Rome III criteria (evaluated by a pre-designed questionnaire based on the Rome III criteria [45] for functional gastrointestinal diseases and validated for Brazilians), [46] and 3- self-reported food intolerance using an adaptation of a previously developed and validated questionnaire. The included items were self-reported gluten (gastrointestinal symptoms after ingestion of foods containing gluten in the last 12 months) and self-reported food intolerance in general

(gastrointestinal symptoms after ingestion of three or more foods in the last 12 months), including gluten foods. The evaluated food items were: non-dairy cream, wheat flour, cow's milk, soy, breads, ice cream, ready sauces, broth, sweets and chocolate. The gastrointestinal symptoms evaluated are abdominal pain, diarrhea, constipation, bloating, flatulence and nausea, recognized gluten-related symptoms as demonstrated in previous studies. The inclusion criteria for the study were a diagnosis of IBS, age 18–70 years old and negative report of medical consultation (GI) in the last 18 months due to gastrointestinal symptoms. The exclusion criteria were clinical suspicion or diagnosis of organic disease of the gastrointestinal tract, including positives stool examination for ova and parasites (Brazil

is an endemic area for parasitic infections). After evaluation of clinical history and the application of Roma III criteria for IBS (recurrent abdominal pain or discomfort during the last six months. These symptoms should be present on three or more days a month associated with two or three of the following situations: improvement with defecation, onset associated with a change in frequency of stool and/or onset associated with a change in shape of stool) [7] the 400 selected volunteers were divided into two groups. The Group I consisted of 87 volunteers with a diagnosis of IBS in accordance with the Rome III criteria (65 women; mean age 30.4±12), Group II consisted of 313 volunteers with no IBS diagnosis (215 women; mean age 36.6±21) and were considered as controls.

Ethics This study was conducted in accordance with the Declaration of Helsinki. All volunteeers gave their informed consent for inclusion before they participated in the study and the protocol was approved by the Regional Committee for Medical and Health Research Ethics, Niteroi, Rio de Janeiro, Brazil (approval no. 93546518.8.0000.5243).

Statistical analysis Statistical analysis was performed using IBM Corp. Released 2017. IBM SPSS

statistics for windows, version 25.0. Armonk, NY: IBM corp. Analysis of categorical data was summarized by descriptive statistics, including total numbers, percentages and odds ratio (OR). The correlation analysis between variables was performed using Pearson's chi-square correlation coefficient. Continuous variables were summarized by mean and standard deviations (SD) with significant differences between two groups analyzed using the Independent Samples t-test. All statistical hypotheses were tested at 0.05 level of significance, and $p<0.05$ was considered significant.

3 RESULTS

Among 400 volunteers (345 females and 55 males) who are available to be analyzed, 87 (21.7%), [mean age 30.4±12.65 (77.4%) females] fulfilling the Rome III criteria for IBS. 47 (54.0%) of them reported gastrointestinal symptoms after ingestion of food in general (gastrointestinal symptoms after ingestion of three or more foods) and 28 (32.1%) volunteers reported gluten intolerance (gastrointestinal symptoms after ingestion of gluten-containing foods), 14 (50%) of which reported no intolerance to foods other than gluten. They were named as Group I. 313 volunteers not fulfilling the Rome III criteria for IBS [mean age 36.6±21, 215 (68.6%) females], 66 (21%) reported food intolerance in general and 50 (15.9%) gluten intolerance. 19 (38%) of them reported only gluten intolerance. They were named as Group II non-IBS. In the two groups positive responses for food intolerance in general were not concentrated in one or two foods, but dispersed in various foods present in the Brazilian dietary pattern. None of the volunteers with IBS and non-IBS reported intolerance to any isolated food.

There was no significant difference in the mean age between the two groups evaluated (p=0.2503), (p>0.05). IBS was most frequent among females, but the number of female evaluated were not statistically different when the two groups were compared. (OR 1.3, 95%CI 0.78-2.30, (p>0.05).

However, the number of positive responses regarding food intolerance in general (gastrointestinal symptoms after ingestion of three or more foods) was higher in Group I when compared to Group II. (OR 4.3, 95%CI 2.66-7.26) p<0.000.1). The self-report gluten intolerance was also significantly different between the two groups (OR 1.8, 95%CI 1.11-3.19 (p=0.0007), (p<0.05).

4 DISCUSSION

In the present study, we evaluated the prevalence of self-reported gluten sensitivity (SRG) in a group of non-patient volunteers from a Brazilian community, who were divided into two groups: IBS and non-IBS. This design was chosen to obtain a sample that would not comprehend outpatients or inpatients, but would rather represent the general population and could provide additional inrmation on the prevalence of IBS in our geographic region.

The prevalence of IBS was not specified as the objective in the study because it is affeted by the inclusion criteria and the number of participants and the results of this study are partial. However, since there is a limitation of data on the prevalence of IBS in South America, we consider the disclosure of information relevant. In this study, we found a 21.7% prevalence of IBS in the volunteers evaluated. In a previous study conducted in Brazil, we reported that the prevalence of symptoms compatible with the diagnosis of IBS was 14.8% [5]. The contrast between the two studies underscores the importance of standardizing diagnostic criteria and the type of population studied, emphasizing the need for more rigorous IBS prevalence studies in South America.

No significant differences were found in the mean age or the gender between the two groups evaluated. However, out of the total number of volunteers evaluated in the study, 280 (70%) were women. These findings introduce a relevant question. Do women pay more attention to their own health, seek more health services, and agree to participate in medical research more often than men? The answer is affirmative and deserves further studies on the subject. In a recent study, we reported that the number of patients undergoing endoscopic procedures (ED) are women and the prevalence of dyspeptic symptoms and the percentage of normal esophagogastroduodenoscopy were significantly higher in women than in men [47].

Despite the limitations of the study and the insufficient number of volunteers evaluated, our preliminary results show that the self-diagnosis percentage of gluten intolerance is higher in volunteers diagnosed with IBS and associated with food intolerance in general.

When we evaluated the groups in relation to prevalence of food intolerance in general (gastrointestinal symptoms after ingestion of three or more foods), we found that the number of

positive responses regarding food intolerance in general was higher in volunteers with IBS diagnosis when compared to Group II. These results are in agreement with most studies [12-17,22,48,49]. Regarding the prevalence of self-diagnosed gluten intolerance (gastrointestinal symptoms after ingestion of gluten containing-foods) in two groups studied, we also found that the number of IBS volunteers that reported gastrointestinal symptoms after ingestion of foods containing gluten differed significantly from the non-IBS volunteers.

These results also confirm that NCGS and IBS are common and both can coexist in a significant portion of the general adult population [22,28-35,37,50-52]. However, symptoms related to FODMAPs share the same clinical characteristics associated with NCGS in individuals with IBS and non-IBS. Thus, IBS-associated symptoms may be triggered by FODMAPs rather than gluten itself [43,47,53-55,57,58].

In addition, the concept of self-reported gluten sensitivity has stimulated the high frequency of self-diagnosis and the growing interest in gluten-free diets [22,55,56]. This rapid increase in popularity of consuming gluten free diet is driven by many factors, including consumer-directed marketing by manufacturers. In the USA, more than $15.5 billion was spent on retail sales of gluten free food in 2016, which is more than double that spent in 2011 [22,53-56]. Gluten and other wheat proteins (e.g. amylase trypsin inhibitors (ATI)) are identified as possible factors for the generation and or exacerbation of IBS symptoms and may interfere with barrier functions.

However, the prolonged gluten restriction may have adverse health effects. There are clear disadvantages of the gluten-free diet itself in relation to adequate nutrition, quality of life, costs, possible heavy metal contamination and also mycotoxin contamination [28,53-59]. These findings have therapeutic implications for IBS patients who identify the intake of gluten foods that trigger their symptoms [40-44].

5 CONCLUSION

The boundaries between CD, wheat allergy, IBS and NCGS are not always clearly distinguishable, and the frequency and clinical identity of NCGS are unclear. Careful planning of clinical trials will lead to a better understanding of the nature of NCGS and its association with IBS. The need for a better clinical understanding of the nature of NCGS, including its trigger, diagnosis, treatment and risks, justifies the recent increase in research on gluten-related diseases.

REFERENCES

1. Sperber AD, Demitasse D, Fu kudo S, Gerson C, Goshala UC, Gee KA, et al. The global prevalence of IBS in adults remains elusive due to the heterogeneity of studies: a Rome Foundation working team literature review. Gut. 2017;66:1075-82.

2. Lovell RM, Ford AC. Global prevalence of and risk factors for irritable bowel syndrome: a meta-analysis. Clin Gastroenterol Hepatol. 2012;10:712-721.e4

3. Canavan C, West J, Card T. The epidemiology of irritable bowel syndrome. Clin Epidemiol. 2014;6:71-80.

4. Soares RL. Irritable bowel syndrome: A clinical review. World J Gastroenterol. 2014;20:12144-60.

5. Soares RL, dos Santos JM, Rocha VR. Prevalence of irritable bowel syndrome in a Brazilian Amazon community. Neurogastroenterol Motil. 2005;17:883.

6. Husain N, Chaudhry IB, Jafri F, Niaz SK, Tomenson B, Creed F. A population-based study of irritable bowel syndrome in a non Western population. Neurogastroenterol Motil. 2008;20:1022-9.

7. Tanaka Y, Kanazawa M, Fukudo S, Drossman DA. Biopsychosocial model of irritable bowel syndrome. J Neurogastroenterol Motil. 2011;17:131-9.

8. Camilleri M, Lasch K, Zhou W. Irritable bowel syndrome: methods, mechanisms, and pathophysiology. The confluence of increased permeability, inflammation, and pain in irritable bowel syndrome. Am J Physiol Gastrointest Liver Physiol. 2012;303:G775-G785.

9. Petitpierre M, Gumowski P, Girard JP. Vernia P, Marinaro V, Argnani F, et al. Self-reported milk intolerance in irritable bowel syndrome: what should we believe? Clin Nutr. 2004;23:996-1000.

10. Yang J, Fox M, Cong Y, Chu H, Zheng X, Long Y, et al. Lactose intolerance in irritable bowel syndrome patients with diarrhoea: the roles of anxiety, activation of the innate mucosal immune system and visceral sensitivity. Aliment Pharmacol Ther. 2014;39:302-11.

11. Dainese R, Casellas F, Mariné-Barjoan E, Vivinus-Nébot M, Schneider SM, Hébuterne X,Piche T. Perception of lactose intolerance in irritable bowel syndrome patients. Eur J Gastroenterol Hepatol. 2014;26:1167-75.

12. Dugum M, Barco K, Garg S. Managing irritable bowel syndrome: The low-FODMAP diet. Cleve Clin J Med. 2016;83:655-62.

13. Volta U, Pinto-Sanchez MI, Boschetti E, Caio GP, De Giorgio R, Verdu EF. Dietary triggers in irritable bowel syndrome: Is there a role for gluten. J Neurogastroenterol Motil. 2016;22:547-57.

14. Mansueto P, D'Alcamo A, Seidita A, Carroccio A. Food allergy in irritable bowel syndrome: The case of non-celiac wheat sensitivity. World J Gastroenterol. 2015;21:7089-109.10

15. Staudacher H, Lomer MC, Lindsay JO, Irving PM, Whelan K. The impact of low FODMAP dietary advice and probiotics on symptoms in irritable bowel syndrome: A randomised, placebo-controlled, 2 × 2 factorial trial. Gut. 2015;64:A51.

16. Monsbakken KW, Vandvik PO, Farup PG. Perceived food intolerance in subjects with irritable bowel syndrome-- etiology, prevalence and consequences. Eur J Clin Nutr. 2006;60:667-72.

17. Eswaran S, Tack J, Chey WD. Food: the forgotten factor in the irritable bowel syndrome. Gastroenterol Clin North Am. 2011;40:141-62.

18. Vazquez-Roque MI, Camilleri M, Smyrk T, Murray JA, Marietta E, O'Neill J, et al. A controlled trial of gluten-free diet in patients with irritable bowel syndrome-diarrhea: effects on bowel frequency and intestinal function. Gastroenterology. 2013;144:903-11.e3.

19. Zanwar VG, Pawar SV, Gambhire PA, Jain SS, Surude RG, Shah VB, et al. Symptomatic improvement with gluten restriction in irritable bowel syndrome: a prospective, randomized, double blinded placebo controlled trial. Intest Res. 2016;14:343-50.

20. Valeur J, Røseth AG, Knudsen T, Malmstrøm GH, Fiennes JT, Midtvedt T, Berstad A. Fecal Fermentation in Irritable Bowel Syndrome: Influence of Dietary Restriction of Fermentable Oligosaccharides, Disaccharides, Monosaccharides and Polyols. Digestion. 2016;94:50-6.
21. Valeur J, Småstuen MC, Knudsen T, Lied GA, Røseth AG. Exploring Gut Microbiota Composition as an Indicator of Clinical Response to Dietary FODMAP Restriction in Patients with Irritable Bowel Syndrome. Dig Dis Sci. 2018;63:429-36.

22. Soares RLS. Irritable bowel syndrome, food intolerance and non- celiac gluten sensitivity. A new clinical challenge. Arq Gastroenterol. 2018;55:417-22.

23. Sapone A, Bai JC, Ciacci C, Dolinsek J, Green PH, Hadjivassiliou M, Kaukinen K, Rostami K, Sanders DS, Schumann M, et al. Spectrum of gluten-related disorders: Consensus on new nomenclature and classification. BMC Med. 2012;10:13.

24. Catassi C, Bai JC, Bonaz B, Bouma G, Calabrò A, Carroccio A, et al. Non-Celiac Gluten Sensitivity: The New Frontier of Gluten Related Disorders. Nutrients. 2013;5:3839-53.25. 25- Soares RLS. Celiac Disease or Gluten Related Disorders? Who Would be the Disease of the Time? Arq Gastroenterol. 2015;52:165-6.

26. Ellis A, Linaker BD. Non-coeliac gluten sensitivity? Lancet. 1978;1:1358-9.

27. Catassi C, Elli L, Bonaz B, Bouma G, Carroccio A, Castillejo G, et al. Diagnosis of Non-Celiac Gluten Sensitivity (NCGS): The Salerno Experts' Criteria. Nutrients. 2015;7:4966-77.

28. van Gils T, Nijeboer P, IJssennagger CE, Sanders DS, Mulder CJ, Bouma G. Prevalence and Characterization of Self-Reported Gluten Sensitivity in The Netherlands. Nutrients. 2016;8:714.

29. Volta U, Bardella MT, Calabro A, Troncone R, Corazza GR. An Italian prospective multicenter survey on patients suspected of having non-celiac gluten sensitivity. BMC Med. 2014;12:85.11

30. Lopez-Gallardo JA, Vergara-Jimenez MJ, Cabrera-Chavez F. Self-reported prevalence of symptomatic adverse reactions to gluten and adherence to gluten-free diet in an adult mexican population. Nutrients. 2015;7:6000-15.

31. Biesiekierski JR, Newnham ED, Shepherd SJ, Muir JG, Gibson PR. Characterization of adults with a self-diagnosis of nonceliac gluten sensitivity. Nutr Clin Pract. 2014;29:504-9.

32. Pinto-Sánchez MI, Verdú EF. Non-coeliac gluten sensitivity: are we closer to separating the wheat from the chaff? Gut. 2016;65:1921-2.

33. Biesiekierski JR, Iven J. Non-coeliac gluten sensitivity: piecing the puzzle together. United European Gastroenterol J. 2015;3:160-5.

34. Aziz I, Branchi F, Sanders DS. The rise and fall of gluten! Proc Nutr Soc. 2015;74:221-6.

35. Skodje GI, Sarna VK, Minelle IH, Rolfsen KL, Muir JG, Gibson PR, et al. Fructan, Rather Than Gluten, Induces Symptoms in Patients With Self-Reported Non-Celiac Gluten Sensitivity. Gastroenterology. 2018;154:529-39.e2.

36. Staudacher H, Lomer MC, Lindsay JO, Irving PM, Whelan K. The impact of low FODMAP dietary advice and probiotics on symptoms in irritable bowel syndrome: A randomised, placebo-controlled, 2 × 2 factorial trial. Gut. 2015;64:A51.

37. Shahbazkhani B, Sadeghi A, Malekzadeh R, Khatavi F, Etemadi M, Kalantri E, et al. Non-Celiac Gluten Sensitivity Has Narrowed the Spectrum of Irritable Bowel Syndrome: A Double-Blind Randomized Placebo-Controlled Trial. Nutrients. 2015;7:4542-54.

38. El-Salhy M, Gundersen D. Diet in irritable bowel syndrome. Nutr J. 2015;14:36.

39. Zeissig S, Kim SJ, Barisani D, Wieser H, Leffler DA, Zevallos V, et al. Wheat amylase trypsin inhibitors drive intestinal inflammation via activation of toll-like receptor 4. J Exp Med. 2012;209:2395-408.

40. Chang JY, Talley NJ. An update on irritable bowel syndrome: from diagnosis to emerging therapies. Curr Opin Gastroenterol. 2011;27:72-8.

41. DiGiacomo DV, Tennyson CA, Green PH, Demmer RT. Prevalence of gluten-free diet adherence among individuals without celiac disease in the USA: results from the Continuous National Health and Nutrition Examination Survey 2009-2010. Scand J Gastroenterol. 2013;48:921-5.

42. Caminero A, McCarville JL, Zevallos VF, Pigrau M, Yu XB, Jury J, et al. Lactobacilli Degrade Wheat Amylase Trypsin Inhibitors to Reduce Intestinal Dysfunction Induced by Immunogenic Wheat Proteins. Gastroenterology. 2019;156:2266-80.

43. Biesiekierski JR, Peters SL, Newnham ED, Rosella O, Muir JG, Gibson PR. No effects of gluten in patients with self-reported non-celiac gluten sensitivity after dietary reduction of fermentable, poorly absorbed, short-chain carbohydrates. Gastroenterology. 2013;145:320-8.e1-3.

44. Valitutti, F, Fasano A. Breaking Down Barriers: How Understanding Celiac Disease Pathogenesis Informed the Development of Novel Treatments. Dig Dis Sci. 2019;64:1748.12

45. Drossman DA. Rome III: the functional gastrointestinal disorders. Gastroenterology. 2006;130:1377-90.

46. Apêndice B. Os critérios diagnósticos de Roma III para os distúrbios gastrointestinais funcionais. Arq Gastroenterol. 2012;49 (Suppl 1):64-8.

47. Soares R, Costa MC, Santos MS, Baliero NDP, Silva TF, Paes J, MenezesGM. Prevalence of negative endoscopic findings in women with dyspeptic symptoms in a Brazilian Community: September 2017 DOI: 10.13140/RG.2.2.31973.50404. https://www.researchgate.net/

48. Soares RL, Figueiredo HN, Santos JM, Oliveira RF, Godoy RL, Mendonca FA. Discrepancies between the responses to skin prick test to food and respiratory antigens in two subtypes of patients with irritable bowel syndrome. World J Gastroenterol. 2008;14:3044-8.

49. Soares RL, Figueiredo HN, Maneschy CP, Rocha VR, Santos JM. Correlation between symptoms of the irritable bowel syndrome and the response to the food extract skin prick test. Braz J Med Biol Res. 2004;37:659-62.

50. Dugum M, Barco K, Garg S. Managing irritable bowel syndrome: The low-FODMAP diet. Cleve Clin J Med. 2016;83:655-62. 51. Vazquez-Roque MI, Camilleri M, Smyrk T, Murray JA, Marietta E, O'Neill J, et al. A controlled trial of gluten-free diet in patients with irritable bowel syndrome-diarrhea: effects on bowel frequency and intestinal function. Gastroenterology. 2013;144:903-11.e3.

52. Zanwar VG, Pawar SV, Gambhire PA, Jain SS, Surude RG, Shah VB, et al. Symptomatic improvement with gluten restriction in irritable bowel syndrome: a prospective, randomized, double blinded placebo controlled trial. Intest Res. 2016;14:343-50.

53. Zitierweise Reese I, Schäfer C, Kleine-Tebbe J, Ahrens B, Bachmann O, Ballmer-Weber B, et al. Non-celiac gluten/wheat sensitivity(NCGS) – a currently undefned disorder without validated diagnostic criteria and of unknown prevalence. Positionstatement of the task force on food allergy of the German Society of Allergology and Clinical Immunology (DGAKI). Allergo J Int. 2018;27:147-51
.
54. Bulka CM, Davis MA, Karagas MR, Ahsan H, Argos M. The Unintended Consequences of a Gluten-free Diet. Epidemiology. 2017;28:e24-e559.

55. Pfeiffer K, Kohlenberg-Müller K. Was kostet eine glutenfreie Ernährung bei Zöliakie? Verzehrserhebungen und Selbsteinschätzungen zum diätetisch bedingten Aufwand. Aktuel Ernahrungsmed. 2015;40:P1.

56. Raehsler SL, Choung RS, Marietta EV, Murray JA. Accumulation of Heavy Metals in People on a Gluten-Free Diet. Clin Gastroenterol Hepatol. 2018;16:244-51.

57. Valitutti F, De Santis B, Trovato CM, Montuori M, Gatti S, Oliva S, Brera C, Catassi C. Assessment of Mycotoxin Exposure in Breastfeeding Mothers with Celiac Disease. Nutrients. 2018;10(3).