REVIEW ARTICLE

Does a Gluten-free Diet Improve Metabolic Syndrome Parameters? A Systematic Review

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Abstract

To review scientific evidence on the effects of a gluten-free diet on body composition and improvement of clinical and biochemical parameters of metabolic syndrome. The Preferred Reporting Items for Systematic Reviews and Meta-Analyzes - PRISMA guidelines were followed. A literature search was performed in the PubMed, ScienceDirect, Trip Database, Bireme and Scielo databases, without language restriction, until March 2021. The terms "gluten-free diet", "obesity", "metabolic syndrome", and "weight loss", and Boolean operators (AND/OR) were used. The clinical hypothesis was structured according to the acronym PICOT. Randomized clinical trials with adult and elderly humans without a diagnosis of celiac disease, consuming a gluten-free diet, evaluating associations of the effects of this diet on weight loss and metabolic syndrome components were considered eligible. To assess the risk of bias, the RoB2 was used. A total of 3,198 articles were identified and, after the screening and evaluation of pre-defined eligibility criteria, four studies were included in the qualitative analysis. Weight loss was not associated with a gluten-free diet. However, individuals under a gluten-free diet had lower mean waist circumference, fat percentage (-2.3%) and serum triglyceride levels. The impact of a gluten-free diet on metabolic syndrome parameters is still controversial. In individuals without gluten sensitivity or celiac disease, the consumption of a gluten-free diet appears to provide no nutritional benefit.

Keywords

Gluten-free diet; Obesity; Metabolic syndrome; Weight loss.

Introduction

Excess adipose tissue is one of the fundamental factors for the release of proinflammatory products and development of insulin resistance. Then, the control of adipose tissue expansion can help in the management of clinical and metabolic parameters involved in metabolic syndrome (MS).

According to the National Cholesterol Education Program and the Adult Treatment Panel III (NCEP-ATP III), MS represents the combination of at least three of the following conditions: waist circumference ≥95 cm, fasting glucose >100mg/dL, plasma triglyceride >150 mg/dL, systolic blood pressure ≥130 mmHg and diastolic blood pressure ≥ 85 mmHg, and HDL cholesterol <40mg/dL).[1] These criteria are also adopted by the I Brazilian Guidelines on diagnosis and treatment of metabolic syndrome[2] and the American Heart Association.[3]

The management of MS has been focused on attenuating modifiable risk factors, including overweight/obesity and changes of lifestyle (mainly diet), thereby contributing to the reduction of its incidence and complications.[4] Dietary strategies that have been used in the management of MS include the traditional Mediterranean diet (MD) characterized by a high intake of cereals, vegetables, and olive oil, a moderate intake of fish and alcohol, a low intake of dairy products, red meat, and sweets;[5,6] and the ketogenic diet, composed of 55-65% of fat, less than 20% of carbohydrates and 25-35% of proteins; the lactose-free diet, and the gluten-free diet (GFD).[7]

Gluten is an insoluble protein complex, obtained during hydration of two cereal proteins, gliadin and glutenin. It is found in wheat, rye and barley and is source of several nutrients.[8] A GFD excludes foods containing

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gluten, mainly wheat, which would promote control of body weight, by reducing adipose tissue and adipocyte size,[9-11] and thereby lead to improvement of clinical and biochemical parameters of MS.

The aim of the present study was to review scientific evidence on the effects of a GFD on body composition and on MS-related clinical and biochemical parameters.

Methods

Study protocol and Registry

The study protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO, registration number CRD42019129789), and the systematic review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses – PRISMA.[12]

Data selection

A literature search for eligible studies was performed in the following databases - PubMed, ScienceDirect, TripDatabase, Bireme and Scielo. The search was conducted until March 2021, without language restriction, using the Medical Subject Headings (MeSH) entry terms, combined using Boolean operators (AND, OR and/or NOT). The search strategy followed the criteria of each database, focusing on the following – *dieta livre de glúten* OR *gluten free diet* AND *obesidade* OR *obesity*; *dieta livre de glúten* OR *gluten free diet* AND *síndrome metabólica* OR *metabolic syndrome*; *dieta livre de glúten* OR *gluten free diet* AND *perda de peso* OR *weight loss*.

Eligibility criteria

Articles were considered eligible if they fulfilled the following criteria – original studies with male and female adults and older adults without a diagnosis of celiac disease, following a GFD, evaluating the effects of this diet on weight loss and MS components. Only randomized clinical trials were included in this review. Observational studies, non-randomized studies, qualitative studies, non-original articles, animal experimental studies and human studies that did not fulfil the inclusion criteria were considered ineligible.

The research question was framed using the PICOT format – Patient (adult patients without celiac disease or gluten intolerance); Intervention (GFD); Comparison (adults and older adults on a diet containing gluten); Outcome (weight loss and changes in MS parameters); Type of study (randomized clinical trial).[13]

Data extraction

Data extraction was done by three reviewers independently. First, the reviewers screened titles and abstracts for eligibility, and then inclusion criteria were applied to the full text of retrieved papers. Disagreements were resolved by consensus or a third reviewer. The following data were extracted – author information, year of publication, author country, number of patients, characteristics of the population, type of intervention, and results related to anthropometric, clinical, and biochemical parameters of MS.

Risk of bias assessment

Three researchers assessed, independently, the risk of bias of the studies included using the Cochrane Collaboration's tool.[14] Discrepancies about the risk of bias were resolved by consensus, or by a consulting a fourth person. The version 2 of the Cochrane risk-of-bias tool (RoB 2) is the recommended tool to assess the risk of bias in randomized trials. The RoB 2 provides a framework for considering the risk of bias in the finding of the randomized trials. The instrument has five domains, as follows: bias arising from the randomization process; bias due to deviations from intended interventions; bias due to missing outcome data; bias in measurement of the outcome; and bias in selection of the reported result. Each risk of bias was judged as "high risk", "low risk" or "some concerns".

Results

Our initial search identified 3,198 articles. After analysis of titles, abstracts, and full texts, four articles fulfilled the inclusion criteria for the qualitative synthesis and systematic review.

The main data extracted from the studies included in the review are described in Chart 1. One clinical trial was conducted in Brazil and three clinical trials in other countries between 2017 and 2020. The smallest and the largest sample sizes were 21 and 60 patients, respectively.

Considering the bias arising from the randomization process, one study,[15] described the method of randomization in detail and was considered low risk. However, in the study by Ehteshami et al.,[10] patients

Chart 1 – Characteristics of the studies included in the systematic review: "Does a gluten-free diet improve metabolic syndrome parameters? A systematic review". Brazil, 2021.

Authors	Country, year	Design	Population (n)	Characteristics of the population	Eligibility criteria	INTERVENTION	CONTROL	Outcome measures	Main results
JOHNSTON, et al.[16]	United States of America, 2017	Randomized clinical trial	Controls=11 (1M + 10F) Treated=10 (5M + 5F)	Healthy adults Age: 20-75 years BMI = 20-42kg/m²	– Screening for history of food allergies or diet restrictions (including gluten intolerance), insulin use, cigarette use, previous dietary changes or physical activity levels, recent weight gain or loss, and current or recent pregnancy or lactation. Eligibility criteria were not defined.	Energy-restricted (500 kcal) + 125g protein + cereals rich in wheat gluten Time of intervention: 6 weeks	Energy-restricted (500 kcal) + 125g protein + foods prepared using gluten-free commercial pasta N=11	Food intake (macronutrients and fibers) Weight loss Body composition Total cholesterol HDL-cholesterol LDL-cholesterol Triglycerides C-reactive protein Glycemia Insulinemia HOMA –IR Glucagon-like peptide-1 Peptide YY Malondialdehyde	– Food consumption and mean weight loss did not differ between the groups; – Greater fat-free mass was observed in the intervention group - Insulin sensibility improved in the intervention group (<insulinemia) – LDL cholesterol, triglycerides, total cholesterol/HDL cholesterol; and the triglycerides/HDL ratio significantly improved over the study period, with no differences between the groups though – PYY decreased in all participants – GLP-1 decreased in the intervention group – No changes in antioxidant or anti-inflammatory parameters were seen

STEFOSKA-NEEDHAM, et al.[15]	Australia, 2017	Randomized clinical trial	60 patients (46F and 14M) Controls = 30 Treated = 26 (4 withdrawals)	Eligible subjects aged between 18 and 65 years, BMI varying from 25 to 35kg/m^2	Eligible patients: – Individuals with chronic diseases, including diabetes and food allergies – Use of medications known to affect appetite – Restrictive eaters (identified using the Three Factor Eating Questionnaire by Stunkard and Messick).	Low-calorie diet (20% below energy requirements) + 45 g sorghum flaked biscuits) Time of intervention: 12 weeks	Low-calorie diet (20% below energy requirements) + 45 g white wheat flaked biscuits)	Anthropometry: body weight (primary outcome), fat percentage, waist circumference; Food intake /food record (energy and macronutrients); Secondary outcomes: plasma glucose, glycosylated hemoglobin (HbA1c), insulin, total cholesterol, HDL-, LDL-cholesterol), triglycerides, interleukin (IL) -1β, IL-6, IL-8, tumor necrosis factor alpha (TNF-α), high-sensitivity C-reactive protein, and total antioxidant capacity (at 0 and 12 weeks).	– No differences were found in weight loss or any clinical variable between intervention and control groups over time. – Waist circumference and percentage of body fat significantly decreased compared with baseline measures. Regression analysis revealed that weight loss significantly predicted changes in waist circumference and body fat. – Physical activity score was not different between the groups at any time point indicating that physical activity levels had no effect on results

EHTESHAMI, et al.[10]	Iran, 2018	Randomized clinical trial	45 individuals with metabolic syndrome (after 5 withdrawals) Controls = 22 (6M+16F) Treated = 23 (6M+17F)	Age range: 25 - 70 years and body mass index between 25 and 35kg/m^2	Eligible: – Individuals with at least three components of metabolic syndrome. – Not using insulin or other antidiabetic drugs, fat burning and weight loss drugs, multivitamin/ mineral, omega-3, green tea supplements in the past month; – Not using oral contraceptives; – Not being on a weight loss diet in the past month; – Not using antibiotics, corticosteroids, immune-suppressants; – Non-smoking, non-pregnant, non-lactating, non-athletic indviduals	Gluten-free diet (<2grams of gluten per day) Time of intervention: 8 weeks	Maintenance of a regular diet	Body weight, waist circumference, total cholesterol, LDL-cholesterol triglycerides, insulin, HOMA-IR and blood pressure	No differences were seen in weight loss, total cholesterol, LDL cholesterol, insulin, HOMA-IR, systolic blood pressure, or diastolic blood pressure between the groups. Mean waist circumference and plasma triglyceride levels significantly decreased in the intervention group compared with controls. Removal of gluten from the diet also improved glycemic control

SILVA et al.[17]	Brazil, 2020	Single-blind, placebo-controlled, cross-over study	40 healthy postmenopausal women	Overweight or obese women aged from 18 to 50 years (BMI 25.0 – 35.4 kg / m^2)	Not eligible: – Women with suspected or confirmed diagnosis of celiac disease and other gluten-related disorders. – Women with chronic diseases, such as diabetes mellitus, systemic hypertension and chronic renal disease	20 women followed a gluten-free diet and consumed a gluten-free muffin, and 20 women followed a gluten-free diet and consumed a gluten-containing muffin Time of intervention: 4 weeks in each group and 4 weeks of follow-up thereafter (total of 12 weeks)	Participants adopted a gluten-free diet for 8 weeks and consumed a gluten-free muffin or a gluten-containing muffin for 4 weeks, switching muffin type during the subsequent 4 weeks There was no control group consuming a regular diet	Body weight, waist circumference, body composition (fat-free mass and fat mass), resting energy expenditure, inflammatory cytokines (TNF, IL-1 e IL-6)	No differences were observed in body weight, body fat, changes in fat-free mass or resting energy expenditure between the intervention groups. Changes in inflammatory cytokines were not significant after intervention

M: male; F: female; BMI: body mass index.

were not properly screened for gluten sensitivity; in the study by Johnston et al.,[16] randomization process was not clear, and in the study by Silva et al.,[17] blinding was not reported.

Three studies[15-17] were considered to have a low risk of bias due to deviations from intended interventions, since the care provided was consistent with what was described in the study protocol. In the study by Ehteshami et al.,[10] it was not clear whether the intervention was implemented as described in the protocol, due to blinding and screening of participants (Figure 2).

As for the bias due to missing outcome data, three studies[10,15,17] were classified as low risk, since the authors clearly described the reasons for patient dropouts. In contrast, in the study by Johnston et al.,[16] a dropout rate of 50% was observed, and the reasons of exclusion were not well described, resulting in a high risk of bias associated with measurement of the outcome.

Finally, a high risk of bias associated with selection of the reported result was observed in the studies by Johnston et al.[16] and Ehteshami et al.[10] due to high lost-to-follow-up rates, limitations caused by inadequate screening of patients and lack of confirmation of intervention compliance.

The reports with the lowest overall risk of bias were those by Stefoska-Needham et al.[15] and Silva et al.,[17]

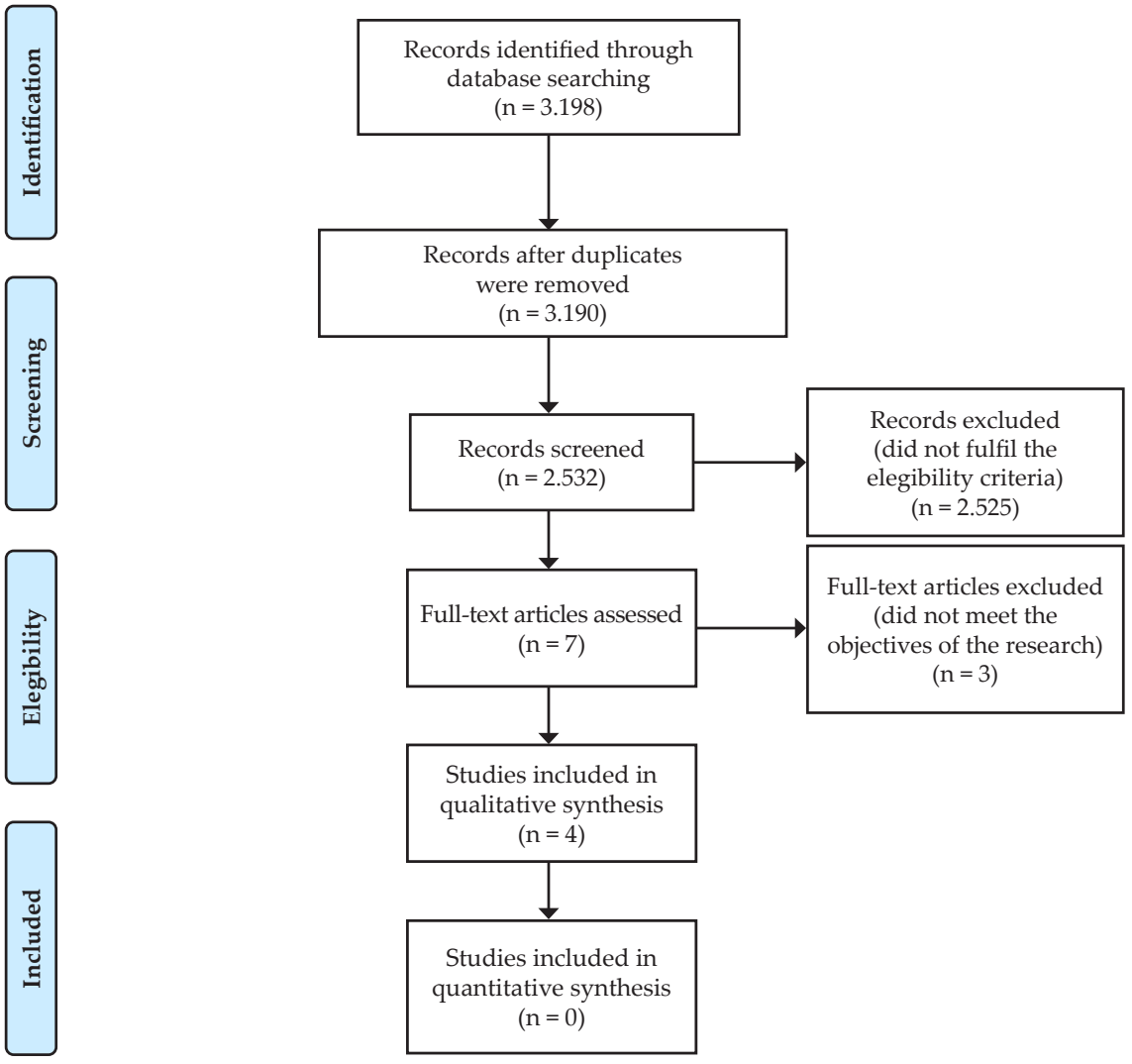

Figure 1 – PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram.
Adapted from Moher et al.[12]

since they answered positively to most of the signaling questions within each domain of bias (Figure 2). The risk of bias and domains of all studies included in this review are summarized in Figure 3.

The studies included in this review compared the effects of a gluten-free diet and a diet containing gluten during an intervention period varying from six to 12 weeks. Two studies[15,16] promoted a reduction in total energy intake, and one study[16] proposed a calorie-restricted, high-protein diet to the intervention group.[16]

In all studies analyzed in this review, GFD was not associated with weight loss, with no statistically significant differences between intervention and control groups. In one study,[16] fat-free mass was greater, and insulin resistance improved in the intervention group (calorie-restricted, high-protein diet, containing gluten) compared with the GFD group.

In two studies,[10,15] mean waist circumference was lower in patients receiving the GFD, and a reduction in body fat percentage (-2.3%) and in serum triglyceride levels were also reported in patients under this dietary strategy.[10]

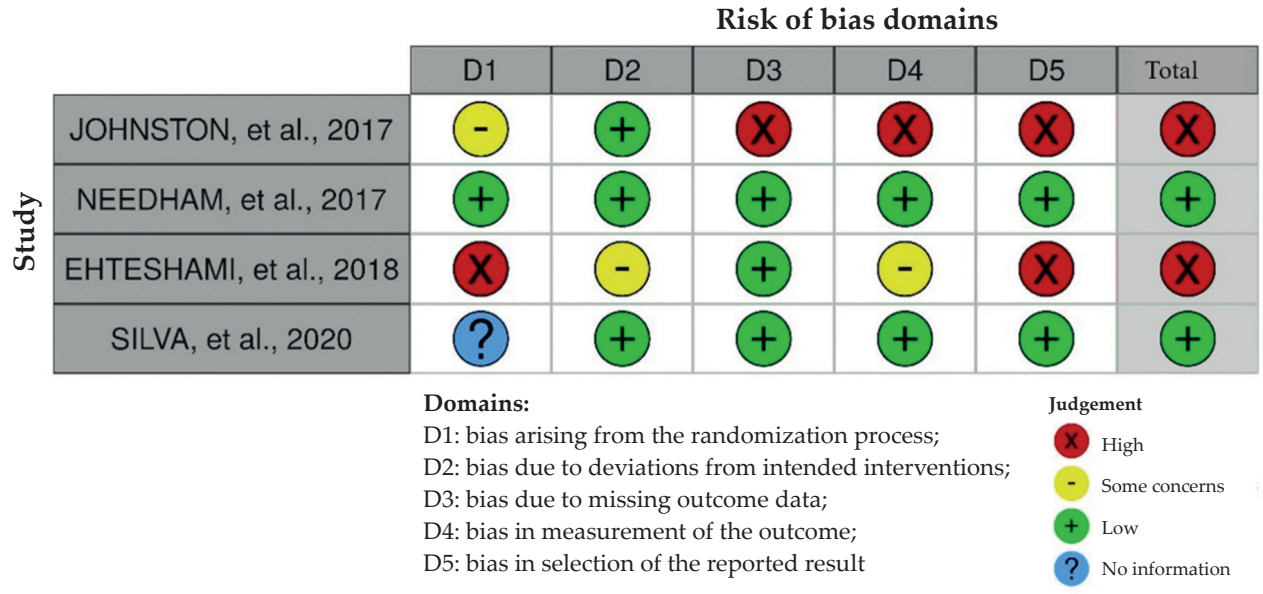

Figure 2 – Risk of bias graph.

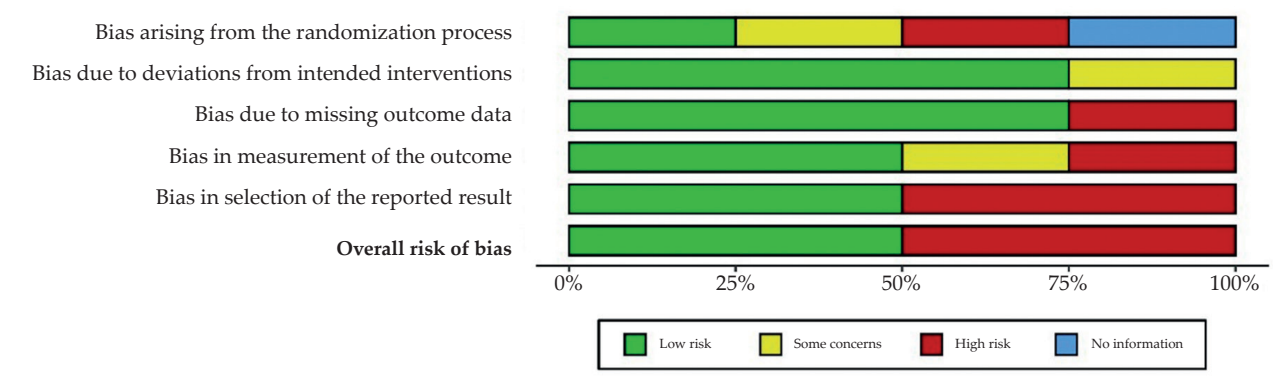

Figure 3 – Summary of the risk of bias of all studies included in the review.

Discussion

For some individuals, a GFD, especially when composed of gluten-free whole grains, is considered a balanced, healthy dietary strategy, and for others, due to its restrictive character, GFD is a valuable strategy for weight loss.[18] Despite the remarkable increase in the adherence to GFDs by the general population over the last five years,[19] and the fact that some authors have suggested that gluten promotes inflammation, and increases the risk of obesity, insulin resistance and MS,[20,21] the findings of the present study do not support an association between weight lost and a GFD.

It is the position of the Brazilian Society of Food and Nutrition (SBAN) that a GFD does not show clear benefits to healthy individuals.[22] A review by Niland and Cash[23] concluded that, apparently, most people who follow a GFD are not gluten sensitive or do not need this diet plan.

The study by Silva et al.,[17] included in this present systematic review did not support the benefit of a GFD. The study[16] was conducted with 40 healthy premenopausal women divided into two groups – 20 women followed a GFD and consumed a gluten-free muffin, and 20 women followed a GFD and consumed a gluten-containing muffin. No differences were observed in body fat, changes in fat-free mass or resting energy expenditure between the intervention groups. Also, the intervention with GFD had no significant effect on inflammatory cytokines.

Despite these findings, over the last years, gluten-free products market has gained importance and enormous popularity among both celiac and nonceliac individuals, drastically increasing the array of gluten-free products, with improved palatability.[23] However, from a nutritional point of view, the lack of evidence supporting beneficial effects of a GFD may be explained by some characteristics of these food products, including a high content of fat, salt, and sugar.[23,24]

In fact, a study conducted by Partichelli et al.[25] with 18 normal weight and overweight individuals, significant increases in serum triglyceride levels were observed after one month of GFD (193.12 ± 135.44 mg/dL vs. 436.54 ± 246.68 mg/dL; $p<0.05$), which is explained by the nutritional composition of gluten-free products. This contrasts with the study by Ehteshami et al.[10] reporting that the use of a GFD diet for weight weeks caused an expressive reduction in triglyceride levels of participants. However, both studies[10,25] demonstrated a significant reduction in waist circumference in individuals receiving a GFD (87.3 ± 14.8 cm vs. 84.5 ± 15.2 cm; $p=0.001$).[25]

A finding that should be highlighted in this systematic review is the increase in fat-free mass and improved glycemic control in the group of patients treated with a low-calorie, high-gluten, high-protein diet, indicating the potential benefits of an energy-restricted hyperproteic diet.

It is known that in dietary management of MS, weight loss is mandatory, which, *per se*, improves insulin sensitivity. In fact, a 5–10% body weight loss, followed by prevention of weight regain, is sufficient to promote clinical benefits.[25]

Therefore, reduction in waist circumference and body fat percentage, and improvements in metabolic parameters (e.g. triglyceride levels) with a GFD are positive and encouraging results. It is worth mentioning, though, that these effects may be more related to the adherence to a healthy diet plan – with calorie restriction, increased consumption of vegetables and fruit, low consumption of sweets and fried foods – than of a GFD.

Also, gluten-free wheat flour, which substitutes conventional wheat flour in the elaboration of gluten-free products, is usually deficient in some macro and micronutrients. For example, rice and corn starches, commonly used in the elaboration of gluten-free cereal products are poor in protein, dietary fiber, and folate. In addition, the production of gluten-free baking products requires the addition of surfactants, such as starch and/or proteinaceous, fatty ingredients like dairy products and egg protein, and gums and s hydrocolloids to compensate the absence of gluten, which may cause nutritional problems, previously described .[2]

When starch is combined with water, at a temperature between 60 and 80°C, gelatinization process occurs, and bread volume increases. However, from a nutritional aspect, foods with more gelatinized starch are highly hydrolysed by α-amylase and have a high glycemic index. Thus, gluten-free products produced with rice or corn starch have a high glycemic index, and its consumption may increase the risk for MS in celiac disease people. Also, it has been shown that the

addition of microencapsulated high-fat powder and low-fat milk powder improves the palatability of gluten-free products but increases their energy content. Besides, gluten-free products are rarely fortified and do not have the same amounts of micronutrients than traditional breads with gluten.[24]

In addition, a gluten containing diet, wheat-based foods naturally contain fructans, oligofructose and inulin. These compounds interact with colonic bacteria and can protect the gut against certain types of neoplasms, inflammatory and cardiovascular diseases, and contribute to the formation of a healthy microbiota. Wheat-derived non-digestible carbohydrates can also reduce postprandial glycemia, insulinemia, fasting triglyceride levels and body weight. Oligofructose has been shown to improve the immune status, lipide metabolism, and the absorption of vitamins and minerals.[26]

As mentioned above, gluten-free manufactured products may have a low protein content as compared with similar products containing gluten, which negatively impact health outcomes.[24] Missbach et al.[27] have shown that the protein content of 57% of the gluten-free food categories analyzed was lower than of the gluten-containing counterparts.

The studies included in this review were carried out in the United States of America. Australia, Iran, and Brazil. According to Melini and Melini,[24] there is no standardized profile for all gluten-free products in the world, with marked differences in the nutritional composition of foods between countries, brands, and food categories. However, according to the authors, there was a consensus among surveys on the lower protein content of gluten-free products than their gluten-containing counterparts.

In addition to the negative impact of their nutritional profile, the cost of gluten-free products is 22-476% higher than conventional food products.[28]

Limitations of the present review include the potential confounding factors of the studies analyzed, such as sex distribution, wide age ranges, different classification criteria for body mass index, small samples, calorie restriction and variable protein intake between groups, which precludes inferring causal relationships between the consumption of a GFD and positive or negative effects on health. Also, the observation time varied from six to 12 weeks between the studies, and whether these effects would be maintained in long term with the use of this strategy is still unknown.

Conclusion

From this review we conclude that a GFD seems not to promote weight loss in individuals without celiac disease. The impact of the GFD on MS parameters is still controversial, as a reduction of triglyceride levels was reported in one study. Therefore, for the general population, with no diagnosis of celiac disease or gluten intolerance, the consumption of gluten-free products in place of traditional foods is associated with higher costs and no apparent benefit from a nutritional perspective. Besides, food and nutrition education are a key element for an adequate diet, which is influenced by several factors related to the food and the act of eating, and achieved by conscious choice, leading to a good nutritional status and better quality of life.

Author contributions

Conception and design of the research: Orange LG, Andrade MIS, Lima CR, Dourado KF, Santos TM, Petribu MM, Silva SA. Acquisition of data: Orange LG, Andrade MIS, Dourado KF, Petribu MM. Analysis and interpretation of the data: Orange LG, Andrade MIS, Lima CR, Dourado KF, Petribu MM, Calaça PRA, Silva SA. Writing of the manuscript: Orange LG, Andrade MIS, Lima CR, Dourado KF, Santos TM, Calaça PRA, Silva SA. Critical revision of the manuscript for intellectual content: Andrade MIS, Lima CR, Silva SA.

Potential Conflict of Interest

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Ethics approval and consent to participate

This article does not contain any studies with human participants or animals performed by any of the authors.

References

1. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). JAMA. 2001;285(19):2486-97. doi: 10.1001/jama.285.19.2486. PMID: 11368702.
2. Sociedade Brasileira de Hipertensão; Sociedade Brasileira de Cardiologia; Sociedade Brasileira de Endocrinologia e Metabologia; Sociedade Brasileira de Diabetes; Sociedade Brasileira de Estudos da Obesidade. I Brazilian guidelines on diagnosis and treatment of metabolic syndrome. Arq Bras Cardiol. 2005;84 Suppl 1:1-28. doi: 10.1590/S0066-782X2005000700001.
3. Grundy SM, Cleeman JI, Daniels SR, Donato KA, Eckel RH, Franklin BA, et al. Diagnosis and Management of the Metabolic Syndrome: An American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. Circulation. 2005;112(17):2735-52. doi: 10.1161/CIRCULATIONAHA.105.169404.
4. Sharovsky LL, Ávila AL, Perez GH, Romano BW. Tratamento Não-Farmacológico da Síndrome Metabólica: Visão do Psicólogo e do Nutricionista. Rev Bras Hipertens. 2005;12(3):182-5.
5. Salas-Salvadó J, Fernández-Ballart J, Ros E, Martínez-González MA, Fitó M, Estruch R, et al. Effect of a Mediterranean diet Supplemented with Nuts on Metabolic Syndrome Status: One-Year Results of the PREDIMED Randomized Trial. Arch Intern Med. 2008;168(22):2449-58. doi: 10.1001/archinte.168.22.2449.
6. Rajaram S, Sabaté J. Nuts, Body Weight and Insulin Resistance. Br J Nutr. 2006;96 Suppl 2:79-86. doi: 10.1017/bjn20061867.
7. Associação Brasileira para o Estudo da Obesidade e da Síndrome Metabólica. Diretrizes Brasileiras de Obesidade 2016. 4th ed. São Paulo: Associação Brasileira para o Estudo da Obesidade e da Síndrome Metabólica; 2016.
8. Vaquero L, Vaquero L, Alvarez-Cuenllas B, Rodríguez-Martín L, Aparicio M, Jorquera F, et al. Revisión de las Patologías Relacionadas con la Ingesta de Glúten. Nutrición Hospitalaria. 2015;31(6):2359-71.
9. Lammers KM, Lu R, Brownley J, Lu B, Gerard C, Thomas K, et al. Gliadin Induces an Increase in Intestinal Permeability and Zonulin Release by Binding to the Chemokine Receptor CXCR3. Gastroenterology. 2008;135(1):194-204.e3. doi: 10.1053/j.gastro.2008.03.023.
10. Ehteshami M, Shakerhosseini R, Sedaghat F, Hedayati M, Eini-Zinab H, Hekmatdoost A. The Effect of Gluten Free Diet on Components of Metabolic Syndrome: A Randomized Clinical Trial. Asian Pac J Cancer Prev. 2018;19(10):2979-84. doi: 10.22034/APJCP.2018.19.10.2979.
11. Wieser H. Chemistry of Gluten Proteins. Food Microbiol. 2007;24(2):115-9. doi: 10.1016/j.fm.2006.07.004.
12. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med. 2009;6(7):e1000097. doi: 10.1371/journal.pmed.1000097.
13. Brasil. Ministério da Saúde. Diretrizes Metodológicas: Elaboração de Revisão Sistemática e Metanálise de Ensaios Clínicos Randomizados. Brasília, DF: Ministério da Saúde; 2012.
14. Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al. Cochrane Handbook for Systematic Reviews of Interventions version 6.2 (updated February 2021). 2nd ed. Chichester (UK): John Wiley & Sons; 2019.
15. Stefoska-Needham A, Beck EJ, Johnson SK, Batterham MJ, Grant R, Ashton J, et al. A Diet Enriched with Red Sorghum Flaked Biscuits, Compared to a Diet Containing White Wheat Flaked Biscuits, Does Not Enhance the Effectiveness of an Energy-Restricted Meal Plan in Overweight and Mildly Obese Adults. J Am Coll Nutr. 2017;36(3):184-92. doi: 10.1080/07315724.2016.1237314.
16. Johnston CS, Sears B, Perry M, Knurick JR. Use of Novel High-Protein Functional Food Products as Part of a Calorie-Restricted Diet to Reduce Insulin Resistance and Increase Lean Body Mass in Adults: A Randomized Controlled Trial. Nutrients. 2017;9(11):1182. doi: 10.3390/nu9111182.
17. Silva RB, Rodrigues É, Coelho BS, Andrade K, Fonseca L, Fernandes-Braga W, et al. Inconsistent Effects of Gluten on Obesity: Is There a Role for the Haptoglobin Isoforms? Clin Nutr ESPEN. 2020;40:269-276. doi: 10.1016/j.clnesp.2020.09.008.
18. Rostami K, Bold J, Parr A, Johnson MW. Gluten-Free Diet Indications, Safety, Quality, Labels, and Challenges. Nutrients. 2017;9(8):846. doi: 10.3390/nu9080846.
19. Valenti S, Corica D, Ricciardi L, Romano C. Gluten-Related Disorders: Certainties, Questions and Doubts. Ann Med. 2017;49(7):569-581. doi: 10.1080/07853890.2017.1325968.
20. Jamnik J, García-Bailo B, Borchers CH, El-Sohemy A. Gluten Intake Is Positively Associated with Plasma α2-Macroglobulin in Young Adults. J Nutr. 2015;145(6):1256-62. doi: 10.3945/jn.115.212829.
21. Soares FL, Matoso RO, Teixeira LG, Menezes Z, Pereira SS, Alves AC, et al. Gluten-Free Diet Reduces Adiposity, Inflammation and Insulin Resistance Associated with the Induction of PPAR-Alpha and PPAR-Gamma Expression. J Nutr Biochem. 2013;24(6):1105-11. doi: 10.1016/j.jnutbio.2012.08.009.
22. Pantaleão LC, Amancio OMS, Rogero MM. Declaração de Posicionamento da Sociedade Brasileira de Alimentação e Nutrição sobre Dieta sem Glúten. São Paulo: Sociedade Brasileira de Alimentação e Ntrução; 2017.
23. Niland B, Cash BD. Health Benefits and Adverse Effects of a Gluten-Free Diet in Non-Celiac Disease Patients. Gastroenterol Hepatol. 2018;14(2):82-91.
24. Melini V, Melini F. Gluten-Free Diet: Gaps and Needs for a Healthier Diet. Nutrients. 2019;11(1):170. doi: 10.3390/nu11010170.
25. Partichelli C, Dorneles G, Peres A. Avaliação do Efeito de uma Dieta com Restrição ao Glúten em Parâmetros Bioquímicos, Estresse Oxidativo, Mcp-1 e Leptina em Indivíduos com Sobrepeso-Obesidade: Estudo Piloto. Rev Bras Obes, Nut e Emagrec. 2019;13(79):370-76.
26. Remes-Troche JM, Cobos-Quevedo OJ, Rivera-Gutiérrez X, Hernández G, de la Cruz-Patiño E, Uscanga-Domínquez LF. Metabolic Effects in Patients with Celiac Disease, Patients with Nonceliac Gluten Sensitivity, and Asymptomatic Controls, After Six Months of a Gluten-Free Diet. Rev Gastroenterol Mex. 2020;85(2):109-17. doi: 10.1016/j.rgmx.2019.02.002.
27. Missbach B, Schwingshackl L, Billmann A, Mystek A, Hickelsberger M, Bauer G, et al. Gluten-Free Food Database: The Nutritional Quality and Cost of Packaged Gluten-Free Foods. PeerJ. 2015;3:e1337. doi: 10.7717/peerj.1337.
28. Panagiotou S, Kontogianni MD. The Economic Burden of Gluten-Free Products and Gluten-Free Diet: A Cost Estimation Analysis in Greece. J Hum Nutr Diet. 2017;30(6):746-52. doi: 10.1111/jhn.12477.