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REVIEW ARTICLE

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Nutritional therapy in celiac disease: a review of the gluten-free diet as a modulator of cardiovascular risk factors

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Abstract

Introduction: Celiac Disease (CD) is a chronic immune-mediated enteropathy precipitated by dietary exposure to gluten in genetically predisposed individuals. The CD has been reported as a rare disease, with an estimated prevalence of 0.3 to 2% worldwide. **Objective:** This study aimed to review the literature on the role of a gluten-free diet in cardiovascular risk factors in patients with celiac disease, specifically related to lipid profile, body mass index, and diabetes mellitus. **Methods:** This is a non-systematic literature review study, carried out from July to October 2017. Relevant publications available in the PubMed and BIREME databases were identified. The literature review included randomized controlled trials, cohort studies, casecontrol studies, and cross-sectional analyses. **Results and Conclusion:** CD it is a disease of special interest due to its association with other autoimmune disorders, intestinal malabsorption, with specific comorbidities, and because its main control mechanism is dietary therapy: the Gluten-Free Diet. Bearing in mind the increase in the worldwide prevalence of celiac disease and its relationship with cardiovascular risk, which may be attributable both to the pathophysiological role of the disease and to the therapeutic plan (dietary), scientific investment in this sphere of public health becomes more than necessary. The influence of gluten-free diet on the cardiovascular risk parameters studied in this review is still not entirely clear. Some studies have suggested that gluten-free diet may have a beneficial effect on the lipid profile of celiac patients, while others have shown that the diet probably does not change or induce atherosclerosis by raising the lipid profile of these patients. In addition, by altering caloric and glycemic intake, the reviewed studies demonstrated a greater tendency towards hyperglycemia and the development of insulin resistance in celiac patients on gluten-free diet. As well as there was a trend towards an increase in body mass index after the introduction of gluten-free diet. However, some authors report that based on these available data, it is not possible to state whether there is a better or worse cardiovascular risk profile after the introduction of gluten-free diet, and therefore, continuity with clinical studies is necessary.

Keywords: Celiac Disease. Gluten-free diet. Cardiovascular risk factors. Metabolic disorders.

Introduction

Celiac Disease (CD) is a chronic immune-mediated enteropathy precipitated by dietary exposure to gluten in genetically predisposed individuals. Evidence suggests that these individuals are positive for the Human Leukocyte Antigen (HLA) system genes DQ2 or DQ8, which are related to the pattern of adaptive immune response mediated by T cells **[1]**.

The CD has been reported as a rare disease, with an estimated prevalence of 0.3 to 2% worldwide. The prevalence of this disease has increased in the USA, as observed in a recent study, which showed a five-fold increase since 1975. Although the reasons for these changes are not clear, they seem to be related to environmental components (changes in the quantity and quality of gluten ingested, infant feeding patterns, the spectrum of intestinal infections, intestinal microbiota colonization, etc.). In addition, a certain increase in prevalence can also be attributed to increased

awareness and improved diagnostic and epidemiological tools **[1,2]**.

Studies have reported a wide variety of clinical manifestations of the disease, including asymptomatic individuals or with intestinal and/or extraintestinal manifestations. Since the 1970s, suspicion of CD has been based on symptoms such as diarrhea, intestinal malabsorption syndrome, and weight loss, known as classic symptoms. However, in recent decades, more and more CD has been diagnosed in its atypical or silent form, and it is often an underdiagnosed condition due to the lack of specificity of the symptoms **[3]**.

The diagnosis of CD is performed by searching for specific antibodies, such as AntiEndomysium, Anti-Tissue Transglutaminase (ATT), and/or Anti-Gliadin Deaminase antibodies. These antibodies strongly support the suspicion of CD but do not confirm the diagnosis. For confirmation, duodenal biopsies are required in the individual still exposed to gluten. Studies report that, on average, around 4-6 biopsies are required for diagnosis **[1,4]**.

Characteristically, it is one of the few diseases treated exclusively with diet. The individual must be placed on a strict Gluten Free Diet (GFD) for life, abstaining from wheat, rye, barley, etc. Therapeutic adherence is difficult for most patients, mainly because there are traces of gluten in almost all refined foods. Furthermore, a strict GFD inevitably restricts the patient's social activities **[5]**.

The chronic inflammatory process involved in the pathogenic mechanism of the disease suggests an increase in cardiovascular risk, especially in individuals not diagnosed early and/or in those who do not adapt to a gluten-free diet. This evidence supports a strong relationship with the genesis of atherosclerosis, with Coronary Artery Disease (CAD) and Ischemic Stroke (IS) being the main consequences of the atherosclerotic mechanism **[6,7]**.

Atherosclerosis has been recognized as a chronic inflammatory condition with the important participation of CD8(+) T cells in its pathophysiological mechanism. The intraepithelial increase of these cells has been a trademark in the development of CD, which underlies the atherogenic role of the disease **[8]**.

Two cohort studies carried out in Scandinavia demonstrate that the risk of developing cardiovascular disease is increased in patients with CD when compared to the general population **[9,10]**. Furthermore, some patients with heart disease and CD showed improved cardiac performance after the introduction of a gluten-free diet **[11]**. The introduction of a gluten-free diet in patients diagnosed with CD has proven to lead to an improvement in intestinal inflammation and nutrient absorption. As a consequence, there is a reduction in serum levels of C-Reactive Protein - CRP, as well as changes in the Body Mass Index (BMI), in the lipid and glycemic profile of these patients, which are known to be important markers of cardiovascular risk. Therefore, it is suggested that GFD has a modulating role in cardiovascular risk in these patients, which justifies this review **[12]**.

This study aimed to review the literature on the role of a gluten-free diet in cardiovascular risk factors in patients with celiac disease, specifically related to lipid profile, body mass index, and diabetes mellitus.

Methods

Study Design and Search Strategy

This is a non-systematic literature review study, carried out from July to October 2017. Relevant publications available in the PubMed and BIREME databases were identified. To achieve the objective of this review, the following terms and their associations were used as keywords: "celiac disease" and "gluten-free diet" and "cholesterol" or "serum lipids" "lipid profile" or "metabolic syndrome" or "cardiovascular risk" or "diabetes mellitus" or "body mass index" or "weight". The detection of these terms was present in the title, abstract, or keywords of the articles. Priority was given to publications from the last five years and/or those most relevant to the topic. Relevant publications were also identified through the bibliography of articles.

The literature review included randomized controlled trials, cohort studies, case-control studies, and cross-sectional analyses. Duplicate articles or those that after reading did not fit the research line were excluded. Few articles fit the line of research, observing a scarcity of studies related to the objective of this work.

Major Results - Revision

Celiac Disease (CD) is characterized by an autoimmune response to gluten in genetically predisposed individuals, giving them chronic inflammatory damage to the mucosa of the small intestine **[1]**. It is a disease of special interest due to its association with other autoimmune disorders, intestinal malabsorption, with specific comorbidities, and because its main control mechanism is dietary therapy: the Gluten-Free Diet (GFD) **[13]**. Furthermore, studies have shown that cardiovascular diseases, including cardiomyopathy, myocarditis, arrhythmias, and premature atherosclerosis are more prevalent in individuals with CD when compared to the general population. A diet based on a GFD may explain, according to some authors, the increased cardiovascular risk in these individuals **[14,15]**.

The pathophysiological mechanism of CD is known to alter the metabolism of micro and macronutrients, cholesterol, and BMI in affected patients, leading to nutritional disorders, cholesterol disorders, and weight disorders. The introduction of GFD for disease control is not a beneficial and consequence-free therapy. Generally, patients are exposed to high-calorie and low-nutrient diets **[16]**. Over the years, researchers have realized that this fact can lead to an increase in BMI, total cholesterol, and important changes in glycemic indexes. All these altered conditions function as additional risk factors in the development of cardiovascular disease, suggesting that its control with GFD may function as a cardioprotective mechanism **[17-21]**.

According to the classic study carried out by Framingham, there is an important correlation between metabolic alterations and the increase in heart disease. Mortality from cardiovascular disease was three times higher in individuals with DM, in addition, these individuals had a higher incidence of heart failure and systemic arterial hypertension **[22]**.

The link between cholesterol and the development of cardiovascular disease has been established since the beginning of the 20th century through incipient animal autopsy studies. In 1977, Gordon and other Framingham scholars reported an inverse relationship between HDL-C levels and the incidence of coronary disease, in contrast to the positive association between LDL concentration and the incidence of coronary disease. In the same year, in collaboration with epidemiological studies carried out in the United States, some researchers reported that individuals with coronary disease had low plasma levels of HDL compared to the healthy population **[23]**.

Obesity usually occurs concomitantly with other metabolic disorders, such as Systemic Arterial Hypertension, cholesterol disorders, and DM, therefore, the increased cardiovascular risk in these individuals is also attributable to the coexistence of these other factors. In addition, even with the control of the coexistence of these factors, obesity is considered an isolated cardiovascular risk factor, conferring a risk two to three times higher compared to the general population **[24]**.

Lipid Profile in CD Patients Submitted to a Gluten-Free Diet

Recent studies have shown that patients with untreated or undiagnosed CD have low levels of cholesterol, especially the High-Density Lipoprotein Cholesterol (HDL-C) fraction. This finding can be explained by the presence of disabsorptive syndrome, reduced cholesterogenesis or reduced Apolipoprotein-A1 secretion, increased biliary secretion, and/or increased fecal cholesterol elimination in these patients. Studies suggest that GFD plays an important role in modulating the lipid profile of celiac patients **[25,26]**.

In a prospective study carried out by Lewis et al **[21]** patients newly diagnosed with CD had their serum cholesterol levels assessed at diagnosis and after 12 months of treatment with GFD. The authors did not observe an increase in total cholesterol with the treatment based on GFD, but they report a significant increase in HDL-cholesterol levels after 12 months of treatment with GFD. De Marchi et al **[12]** analyzed the lipid profile of patients diagnosed with CD before and after dietary treatment (GFD) and observed a beneficial increase in total cholesterol in these patients secondary to the serum increase in the HDL fraction.

Zanini et al. **[27]** performed a retrospective study from January 1990 to July 2011 by collecting blood material to analyze the lipid profile of all patients diagnosed with CD before and during treatment with GFD. This study demonstrated a significant increase in serum total cholesterol levels during treatment with GFD, causing 124 patients (23%) to leave the low cardiovascular risk classification for higher risk categories. The authors report that this increase in total cholesterol values was also accompanied by an increase in the HDL-C fraction. In addition, a decrease in the absolute values of triglycerides was demonstrated during GFD, which meant that 9% of patients had their risk category altered.

However, Tortora et al **[28]** carried out a clinical trial with 98 patients analyzing the parameters of Metabolic Syndrome at the diagnosis of CD and one year after the introduction of therapy with GFD. Concerning the lipid profile of these patients, the study did not demonstrate statistically significant differences when compared to pre- and post-treatment values, which contrasts with the other cited studies that showed an increase in the HDL-C fraction.

BMI in CD Patients Undergoing GFD

In recent decades, numerous studies have demonstrated important changes in the clinical aspects of CD. In particular, the proportion of patients diagnosed as being overweight has been increasingly reported in the literature.

In a study carried out by Ukkola et al **[18]**, in 2011, 698 patients newly diagnosed with CD had their weight measured at diagnosis and one year after treatment with GFD. After one year of dietary treatment, 33% of patients gained and 16% of patients lost at least 3 kg. However, the authors conclude that there was no

significant association between dietary counseling and changes in the patient's BMI, with a tendency towards favorable changes in BMI to the detriment of unfavorable ones. In addition, they suggest that GFD should not be understood as the only factor involved in changes in BMI in these patients, and attention should be paid to other associated conditions and to the type of GFD offered, which may vary between the countries and locations studied.

On the other hand, most studies have proven the important participation of GFD in weight gain in celiac patients. Like the study carried out by Kabbani et al **[17]** in 2012, in which 679 patients had their BMI analyzed before and after GFD and these values were compared with the general population of the United States based on data obtained from the National Health Interview Survey (NHIS). The average evaluation time between the first and last BMI measurements was approximately 39.5 months. Characteristically, the celiac population had lower weight than the general non-celiac population and therefore a lower percentage of individuals in the overweight or obese range. The authors demonstrated that the BMI of the cohort studied increased significantly (24% of patients) after the introduction of GFD ($p<0.001$) and that weight gain was predominantly greater in individuals with lower dietary adherence, suggesting an important risk factor for BMI changes in these patients. Furthermore, regardless of dietary adherence, it has been reported that the longer an individual remains on GFD, the greater the chances of having an increase in their BMI.

Some authors suggest that histological changes in the intestinal mucosa of celiac patients may take more than twelve months for complete recovery. Consequently, this fact can lead to a delay in nutrient absorption and weight recovery in these patients **[29,30]**. This may explain the inconsistencies between some studies, as the follow-up time of patients in different studies is also different.

Evidence shows that GFD can promote significant changes in the BMI of celiac patients. Adherence to therapy was configured as an important risk factor for overweight and obesity as demonstrated by Kabbani et al **[17]**, suggesting the need for effective methods to monitor therapeutic adherence in celiacs and that these methods should be an integral part of the follow-up clinic for these patients.

Weight gain after the onset of GFD has become an important concern for treated celiac patients mainly because it promotes improved nutrient absorption and leads to weight gain **[31]**. With weight gain, the risk of morbidity also increases, that is, metabolic syndrome, type 2 diabetes mellitus, and increased cardiovascular risk **[32]**.

Glycemic profile in patients with Celiac Disease undergoing Gluten-Free Diet

Diabetes Mellitus (DM) is a chronic metabolic disorder and an important risk factor for cardiovascular disease. Its inadequate control is related to the increased incidence of micro and macrovascular diseases **[33]**. The prevalence of Type 1 Diabetes Mellitus (T1DM) in patients with CD is known to be high, as reported by several studies, mainly due to the association between autoimmune diseases. However, few studies have evaluated the presence of Type 2 Diabetes Mellitus (T2DM) in these patients and/or the role of GFD in the glycemic control of patients already diagnosed with CD or as a protective or risk factor in the incidence of DM in these patients **[34,35]**.

A recent study demonstrated that T2DM patients with inadequately controlled glycemic levels have a greater chance of developing CD than the control group, suggesting that glycemic levels may induce the onset of CD in predisposed patients, probably by immunological mechanisms **[34,36]**. On the other hand, a study also recently published with 1365 patients shows that the prevalence of T2DM in individuals with CD is comparable to that of the general population **[37]**.

Some GFD foods characteristically have higher glycemic indexes than their gluten counterparts, but some authors refute this idea **[38]**. The high glycemic indices of gluten-free foods may partially explain the changes found in these patients after 1 year of GFD, which Tortora et al associate with a 4.5 times greater risk of hyperglycemia in patients undergoing dietary therapy. In addition, high values of plasma glucose found in these patients are also indicators of insulin resistance, being a potential risk factor for increased cardiovascular risk in these patients **[28]**.

Tissue Transglutaminase, a characteristically positive autoantibody in CD patients, drives the inflammatory response in these individuals through down-regulation of the Peroxisome Proliferator Gamma Activation Receptor (PPARG) **[39]**. As the up-regulation of PPARG is implicated in susceptibility to T2DM, it is possible that, by reducing inflammation, GFD may also influence this pathway by increasing insulin resistance. However, more studies are needed to prove this theory **[40,41]**.

Conclusion

Bearing in mind the increase in the worldwide prevalence of celiac disease and its relationship with cardiovascular risk, which may be attributable both to

the pathophysiological role of the disease and to the therapeutic plan (dietary), scientific investment in this sphere of public health becomes more than necessary. The influence of gluten-free diet on the cardiovascular risk parameters studied in this review is still not entirely clear. Some studies have suggested that gluten-free diet may have a beneficial effect on the lipid profile of celiac patients, while others have shown that the diet probably does not change or induce atherosclerosis by raising the lipid profile of these patients. In addition, by altering caloric and glycemic intake, the reviewed studies demonstrated a greater tendency towards hyperglycemia and the development of insulin resistance in celiac patients on gluten-free diet. As well as there was a trend towards an increase in body mass index after the introduction of gluten-free diet. However, some authors report that based on these available data, it is not possible to state whether there is a better or worse cardiovascular risk profile after the introduction of glutenfree diet, and therefore, continuity with clinical studies is necessary.

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