

Cardiometabolic risk factors in children with celiac disease on a gluten-free diet

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Abstract

Celiac disease (CD) is an immune-mediated systemic condition evoked by gluten and related prolamines in geneti-

cally predisposed subjects. It is characterised by a variable combination of gluten-dependent clinical symptoms, CD-specific antibodies, HLA-DQ2 and HLA-DQ8 haplotypes, and enteropathy. The only therapy of CD consists of a life-long gluten free diet (GFD). Strict GFD adherence results in full clinical, serological and histological remission, avoiding long-term complications in CD patients. However, this diet is not without problems. Gluten free products have high levels of lipids, sugar and salt to improve food palatability and consistency, and subjects with CD show an excessive consumption of hypercaloric and hyperlipidic foods to compensate dietetic restriction. GFD may therefore have a negative impact on cardiometabolic risk factors such as obesity, serum lipid levels, insulin resistance, metabolic syndrome, and atherosclerosis. In adults, some studies have suggested that GFD have a beneficial effect on cardiovascular profile, whereas others have shown an atherogenic effect of GFD. In children, very few studies are available on the issue. Thus, the aim of the present narrative review was to analyze the current clinical evidence on the impact of GFD on cardiometabolic risk factors in children with CD.

Key words: Celiac disease; Children; Gluten free diet; Cardiometabolic risk; Atherosclerosis

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Core tip: Recent epidemiological studies suggest that gluten free diet (GFD) may have adverse effects on body weight, serum lipid levels and insulin resistance in youths with celiac disease (CD). Screening for cardiometabolic risk factors in celiac children is to be recommended not only at diagnosis but also during follow-up since an early intervention may prevent cardiovascular morbidity. Dietary guidance over time, targeting obesity and other components of metabolic syndrome besides monitoring adherence to GFD may be warranted in CD youths.

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INTRODUCTION

Celiac disease (CD) is an autoimmune systemic condition elicited by ingestion of food containing gluten and related prolamines in genetically predisposed subjects. It is characterized by heterogeneous clinical symptoms and signs, specific antibodies including anti-transglutaminase antibodies (tTGA), HLA-DQ2 and HLA-DQ8 haplotypes, and enteropathy. Genetic, immunological and environmental factors therefore appear to be responsible for the disease. In 90% to 95% of patients with CD is present HLA-DQ2, whereas 5% carry the HLA-DQ8 haplotype, and the remaining 5% at least one of the two DQ2 alleles^[1,2]. CD affects up to 1% of the population in the western world, and has been related to several complications^[3,4].

Nowadays the only accepted treatment is gluten free diet (GFD). It consists in life-long elimination from the diet of gliadin and glutamin proteins, fractions contained in wheat, rye, and barley and hybrids like kamut and triticale. Strict GFD adherence leads to full clinical, serological and histological remission and avoids long-term complications in CD patients^[1,2]. However, this diet is not without problems. Some available reports show that GFD may result in macro- and micronutrient deficiencies; in particular, the dietary intake of patients on GFD is characterized by low levels of fiber, vitamin B, folate, vitamin D, calcium, iron, zinc and magnesium^[5-7]. GFD may also have other important consequences. Overweight and obesity have been added to the list of possible nutritional consequences while on GFD, being partially related to hypercaloric content of commercially available gluten-free foods. Indeed, there is clinical evidence indicating an increased caloric intake as well as higher consumption of fats, saturated fats, simple carbohydrates and food with elevated glycemic index^[8-10] with such diets. Gluten free products have high levels of lipids, sugar and salt to improve food palatability and consistency, and subjects with CD show an excessive consumption of hypercaloric and hyperlipidic foods to compensate dietetic restriction. GFD may therefore have a negative impact on cardiometabolic risk factors such as obesity, serum lipid concentrations, insulin resistance, metabolic syndrome, and atherosclerosis.

Whether GFD affects the cardiovascular risk profile in patients with CD remains under discussion. In adults, some studies have suggested that GFD have a beneficial effect on cardiovascular profile consequently to its anti-atherosclerotic effects^[11,12], whereas others have shown atherogenic effects of GFD^[13,14]. In children, very few studies are available on this topic. Thus, the purpose of the present narrative review was to analyze the current clinical evidence on the impact of GFD on cardiometabolic risk factors in children with CD.

OBESITY

Obesity nowadays is more frequent in CD than in the past. Numerous reports in adults and youths with CD have shown that overweight and obesity is not unusual at diagnosis. The proportion of CD children affected by overweight and obesity at diagnosis is between 8.8% and 20.8% and between 0% and 6%, respectively^[13,15,16]. Also, there is some evidence that GFD may predispose to development of overweight and obesity^[15-18] for several reasons. First, GFD improves intestinal absorption; second, GFD is an unbalanced diet rich in lipids and proteins^[9]; third, CD patients prefer food with elevated caloric fat and protein contents to contrast the GFD unpalatability. The development of increased weight in CD patients may be also linked to the global trend toward overweight and obesity in the pediatric age^[19].

There are multiple reports on the association of GFD and obesity in youths with CD, with conflicting results^[9,13,15-18,20-27]. Mariani *et al*^[9] first reported a higher rate of overweight and obesity in CD adolescents on GFD in comparison with CD subjects on gluten-containing diet and healthy controls (72% vs 51% and 47%). Valletta *et al*^[15] found that the prevalences of overweight and obesity were 11% and 3%, respectively, at diagnosis in 149 youths with CD. After at least 12 mo of GFD, there was a significant increase in the body mass index (BMI) z-score, and the percentage of overweight children almost doubled (11% vs 21%, $P = 0.03$). The proportion of obese patients remained the same (3% vs 4%). In a recent cross-sectional multicenter study, Norsa *et al*^[13] evaluated 114 CD children with negative CD serology after at least 1 year of GFD. They found that 9.6% of youths were underweight, 76.3% had normal weight, and 8.8% were overweight, whereas 5.3% were obese. Both prevalences of overweight and obesity rose up to 11.4% and 8%, respectively, after GFD introduction.

Opposite results were reported by Venkatasubramani *et al*^[26], Brambilla *et al*^[16], Reilly *et al*^[18] and Nenna *et al*^[27]. In a retrospective study including 143 CD subjects diagnosed between 1986 and 2003, Venkatasubramani *et al*^[26] identified 7 (5%) patients with a BMI > 95th percentile. After 1-year GFD, BMI increased in 2 (25%), but decreased in 4 (50%). They, therefore, concluded that GFD in obese CD children may reduce BMI. Brambilla *et al*^[16] compared 150 CD children on GFD (median time, 4.4 years) with 288 age- and sex-matched healthy subjects. They evaluated retrospectively BMI changes since CD diagnosis to the latest clinical assessment, and found that the frequencies of overweight and obesity in CD children at diagnosis and during GFD were significantly lower than those reported in healthy controls. The study by Reilly *et al*^[18] involving 142 pediatric CD patients showed that 19% of subjects at diagnosis presented an elevated BMI (12.6% were overweight and 6% were obese), while 74.5% had a normal BMI. Seventy-five percent of children with high BMI at diagnosis had a significant decrease

in their BMI z-scores on a strict GFD. In particular, 44% of them normalized their BMI z scores. The authors concluded that GFD may have a favorable effect upon the BMI of overweight and obese youths with CD. Finally, in a retrospective study evaluating the prevalence of CD in a large cohort of overweight/obese children and adolescents, Nenna *et al.*^[27] observed that the prevalence of CD (1.11%) was similar to that found in general population. Moreover, they demonstrated that these subjects may benefit from a balanced GFD diet.

SERUM LIPIDS

The consequences of GFD on lipid profile in childhood have been analyzed in several studies. Rosenthal *et al.*^[28] compared plasma lipids and lipoprotein pattern between 12 untreated CD children and 10 control subjects. They found an altered lipid profile characterized by decreased serum triglycerides levels, very low density lipoprotein (VLDL) and apolipoprotein-A-I (apo-A-I), and increased low density lipoprotein cholesterol (LDL-C) in CD children, because of fat malabsorption. On GFD the lipid profile reverted to normal as consequence of improvement of mucosal damage caused by gluten withdraw. Ciampolini *et al.*^[29] investigated the plasma lipid levels in CD children (45 under and 49 over 3 years of age, at diagnosis) on GFD, and in comparison with children affected by irritable bowel syndrome (IBS) matched for body size, gender, and age. They found that untreated CD children had significantly lower total and high density lipoprotein cholesterol (HDL-C) levels and significantly higher triglyceride concentrations than IBS controls in both age groups. A period of GFD increased HDL-C in both age groups, while total cholesterol, LDL-C, and triglyceride levels decreased only in the younger age group. Pillan *et al.*^[30] compared serum lipids and lipoprotein (a) concentration in 17 adult and pediatric CD patients at diagnosis and after 3 mo of GFD. They found that mean total cholesterol and LDL-C did not significantly change, while mean HDL-C significantly rose and mean triglyceride levels significantly decreased after the diet, suggesting that GFD may positively influence lipid profile. Recently, in a cross-sectional prospective study, Forchielli *et al.*^[31] analyzed the impact of GFD on serum lipid concentrations in children with CD compared with the general pediatric population. They studied 235 CD children and adolescents: In 205 patients the lipid profile was available only after diagnosis (group 1), whereas in 30 patients it was available both before and after GFD (group 2). The Authors found that in group 1, total cholesterol, triglyceride, and HDL-C concentrations were significantly elevated in girls in comparison with boys. Furthermore, compared with the general pediatric population, group 1 girls had higher total cholesterol, triglycerides, HDL-C and LDL-C, while group 1 boys had lower total cholesterol, triglycerides and LDL-C, and higher HDL-C. In group 2, total cholesterol did not change over time, triglycerides diminished, and

HDL-C increased. They therefore suggested that GFD, being appropriate in terms of fibers and unsaturated fats^[31], may have a positive influence on lipid profiles, determining higher HDL-C in CD children than in the reference population.

Against this background, Médiène *et al.*^[32], who compared 46 CD adult and pediatric patients and 155 control subjects, found that untreated CD patients had decreased cholesterol, phospholipid and apo-A-I levels and elevated triglycerides. However, they did not find a return towards normal lipid profile following GFD.

INSULIN RESISTANCE

There are only few studies on insulin resistance in both CD adults and youths on GFD. In a retrospective study evaluating the effects of 1-5 years of GFD on markers of cardiovascular risk in a large cohort of adult patients, Zanini *et al.*^[12] found that insulin resistance remained constant from baseline to follow-up. Of note, absolute levels of serum glucose rose from 87.9 mg/dL at baseline to 89.7 mg/dL during GFD ($P = 0.0001$), reaching statistically significance only in females. In a sample of Italian and Israeli CD patients on GFD, Norsa *et al.*^[13] found that 3.5% of 114 children on GFD had insulin resistance. Because of lack of data on insulin values before CD diagnosis, the authors were not able to determine whether insulin resistance could be, indeed, attributed to the start of GFD.

METABOLIC SYNDROME

Data regarding the prevalence of metabolic syndrome (MetS) in patients with CD on free diet or on GFD are still scarce and limited to adults with CD. In an observational prospective study involving 98 adult CD patients, Tortora *et al.*^[33] found that 2% of them fulfilled the diagnostic criteria for MetS at diagnosis while 29.5% after one year of GFD. Among the MetS components, there was a significant increase in BMI, waist circumference, blood pressure and blood glucose levels, whereas no significant difference was detected in the lipid profile from baseline to 12 mo after the introduction of GFD. They concluded that patients with CD on GFD are at risk of developing MetS. In contrast, Kabbani *et al.*^[34] comparing 26 CD adults with 81 controls, reported that MetS is less frequent in CD than in controls (3.5% vs 12.7%, $P < 0.0001$).

Nonalcoholic fatty liver disease (NAFLD), considered as the hepatic component of MetS, is the most frequent cause of chronic liver disease in youths worldwide. Potential triggers for NAFLD including metabolic risk factors (*i.e.*, abdominal adiposity and insulin resistance) as well as altered intestinal permeability may be present in CD patients. However, there are very few reports of NAFLD in subjects with CD. Recently, Reilly *et al.*^[35] compared the risk of NAFLD diagnosed between 1997 and 2009 in 26816 pediatric and adult CD patients with that in 130051 age-, gender-, calendar year-, and

county-matched subjects. They observed a 4.2-fold increased risk of NAFLD in the first five years after diagnosis of CD. This increased risk was mainly due to NAFLD diagnosed in the first year after diagnosis of CD, but was still significantly high 15 years after the diagnosis of CD.

SUBCLINICAL ATHEROSCLEROSIS

Several studies have shown that atherosclerosis begins in childhood and protracts into adulthood^[36,37]. Early detection of arterial damage is fundamental to prevent future vascular risk since subclinical atherosclerosis can be reversible if detected earlier and intervention is provided. Subjects at high risk for cardiovascular disease (CVD) may be identified by determination of arterial thickness and distensibility, endothelial function and proinflammatory and protrombotic state alone or in combination^[38-40]. Altered flow-mediated vasodilatation, as well as increased carotid-artery intimal medial thickness (cIMT) can be assessed by ultrasonography allowing an early diagnosis of preclinical atherosclerosis^[41]. Arterial stiffness can be assessed by pulse wave velocity (PWV) measurement^[42], the main index for estimating arterial elasticity.

Endothelial dysfunction and increased arterial stiffness have been reported in adult patients with CD^[43,44]. To the best of our knowledge, only Demir *et al.*^[45] investigated markers of preclinical atherosclerosis in children with CD. In a cross-sectional study, the authors studied arterial stiffness and thickness using PWV and cIMT in 37 pediatric patients with CD compared to 36 age- and sex-matched healthy controls. A strict adherence to GFD, evaluated by determination of tTGA levels, was detected in 59.4% of 37 CD patients. There was no significant difference between tTGA positive and tTGA negative children in terms of PWV and cIMT. Nonetheless, cIMT was significantly lower in CD subjects adherent to GFD in comparison with healthy controls. Moreover, cIMT was positively associated with tTGA levels in patients with CD, suggesting that lack of dietary compliance in such patients might pave the road to arterial thickness^[43]. These results suggest that GFD is likely to be anti-atherogenic, and that long-term gluten withdrawal might prevent premature atherosclerosis.

CV RISK PROFILE

Several studies have reported an increased risk of CVD as well as an increased risk of death for CVD in CD patients, especially those with untreated CD, in comparison with the general population^[46-50]. In a systematic review and meta-analysis, Emilsson *et al.*^[48] reported that CD was associated with a 10% increased risk of CVD, but some studies did not confirm these data^[49,50]. Of note, it has been suggested that transglutaminases can modulate several cardiovascular risk factors, mainly hypertension, atherosclerosis, vascular permeability and

angiogenesis^[51].

To our knowledge, only two studies have explored the cardiovascular risk profile in children with CD^[13,52]. In a cross-sectional multicenter study involving 114 CD children on GFD, Norsa *et al.*^[13] reported the profile of CVD risk factors including obesity, abdominal obesity, high LDL-C, high triglycerides, hypertension, and insulin resistance. The main prevalent CVD risk factors were elevated triglycerides (34.8%), hypertension (29.4%), and elevated serum levels of LDL-C (24.1%). The Authors found 3 or more coexistent risk factors for CVD in 14% of the entire cohort, whereas absence of risk factors was found in only 30.7% of the cohort. Moreover, significant increments in both total cholesterol and HDL-C were found in CD children on GFD. This is in line with some authors arguing that alteration of intestinal absorption, chylomicron production and lipoprotein metabolism may underlie the presence of lower concentrations of total cholesterol and HDL-C in CD subjects at diagnosis, which can return to normal levels after GFD^[28,52]. They therefore highlight the critical role of screening for cardiovascular risk factors in CD youths at diagnosis as well as at follow-up. Very recently, in a retrospective study Assa *et al.*^[53] found that at the age of 17 years the prevalence of certain CVD risk factors such as hypercoagulability, hyperlipidemia, and type 2 diabetes was higher in adolescents with CD compared to the general population. In contrast, the prevalence of traditional cardiovascular risk factors such as high blood pressure and overweight/obesity was similar between the two groups. However, these findings should be cautiously interpreted since information on age at diagnosis as well as on GFD adherence was not available.

Early cardiac involvement in youths with CD and the impact of GFD on this issue have also been evaluated. Lionetti *et al.*^[54] compared cardiac structure and function before and after 1 year of GFD in 60 children with CD and in a control group of 45 healthy children. There were significantly lower contractility indices, and higher left ventricular dimensions in untreated CD. Notably, these parameters reverted to normal after GFD. Interestingly, GFD, along with immunosuppression, can be effective in CD-associated autoimmune myocarditis^[55].

CONCLUSION

The available literature shows conflicting data on the effects of GFD on cardiometabolic risk factors in children and adolescents with CD. The majority of the studies indicate changes in markers associated with cardiovascular risk. These variations, in any case, do not constantly point at a better or worse cardiovascular risk profile. Limitations of most studies comprise the relatively small sample size, the cross-sectional design that does not permit comparison between pre- and post-GFD values of the evaluated parameters, and the absence of knowledge of familial history for CVD risk factors. Therefore, additional longitudinal, well-

designed studies involving a large number of children with long-term follow-up are necessary to clarify whether prolonged exposure to GFD might result in an increased cardiometabolic risk. At this time, GFD remains the milestone of CD treatment. Nonetheless, an in-depth assessment of nutritional status along with cardiometabolic screening in CD children at diagnosis and during GFD have to be recommended because an early intervention may prevent cardiovascular morbidity. Dietary guidance over time, targeting obesity and other components of MetS besides monitoring adherence to GFD may be warranted in youths with CD.

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