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MINIREVIEWS

Type 1 diabetes and celiac disease: The effects of gluten free diet on metabolic control

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Abstract

Type 1 diabetes mellitus is associated with celiac disease, with a prevalence that varies between 0.6% and 16.4%, according to different studies. After a diagnosis of celiac disease is confirmed by small bowel biopsy, patients are advised to commence a gluten-free diet (GFD). This dietary restriction may be particularly difficult for the child with diabetes, but in Europe (and in Italy) many food stores have targeted this section of the market with better labeling of products and more availability of specific GFD products. Treatment with a GFD in symptomatic patients has been shown to improve the symptoms, signs and complications of celiac disease. However, the effects of a GFD on diabetic control are less well established. Initial reports of improved hypoglycemic control were based on children who were diagnosed with celiac disease associated with malabsorption, but there have subsequently been reports of improvement in patients with type 1 diabetes with subclinical celiac disease. There are other studies reporting no effect, improved control and an improvement of hypoglycemic episodes. Moreover, in this review we wish to focus on low glycemic index foods, often suggested in people with type 1 diabetes, since they might reduce postprandial glycemic excursion and enhance long-term glycemic control. In contrast, GFD may be rich in high glycemic index foods that can increase the risk of obesity, insulin resistance and cardiovascular disease, worsening the metabolic control of the child with diabetes. Hence, it is important to evaluate the impact of a GFD on metabolic control, growth and nutritional status in children with type 1 diabetes.

Key words: Adolescents; Celiac disease; Children; Glycemic control; Type 1 diabetes

Core tip: It is important to evaluate the impact of a gluten-free diet (GFD) on metabolic control, growth and nutritional status in children with type 1 diabetes and celiac disease. Since compliance with a strict GFD and a safe choice of food for diabetes is not easy, these patients require extra education and dietary intervention. A specialized follow-up and dietary counseling are essential in the management of patients affected by both type 1 diabetes and celiac disease.

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INTRODUCTION

Type 1 diabetes is an immune-mediated disorder characterized by a deficit or absence of insulin resulting from T cell-mediated destruction of beta cells of the pancreas[1].

Children with type 1 diabetes have an increased risk of developing other autoimmune disorders like Hashi-

moto's thyroiditis, Addison disease, vitiligo and celiac disease[2]. The relation between type 1 diabetes and these pathologies is a common genetic background. All of these diseases are associated with organ-specific autoantibodies that can be detected before the development of clinical diseases; consequently, patients affected by type 1 diabetes usually undergo a scheduled (usually once a year) screening for these pathologies.

Celiac disease is one of the most common autoimmune disease-based disorders; it is elicited by a failure of oral tolerance towards wheat, gluten and related cereals, which results in a multisystem inflammation of the intestinal tract. It usually develops in HLA-DQ2/8 positive individuals. The first association between type 1 diabetes and celiac disease was suggested in 1969[3]. The genetic risk factors associated with both diseases include human leukocyte antigen (*HLA*) genes and non-*HLA* genes.

The increased prevalence of celiac disease in patients with type 1 diabetes is due to an overlap in the genetic susceptibility to both diseases conferred by the *HLA-DR3/DQ2*[4]. This haplotype is present in over 90% of patients with celiac disease and 55% of those with type 1 diabetes, compared with only 20%-25% of the general population of European ancestry. HLA-DQ8 also confers a risk of type 1 diabetes[4].

Celiac disease affects at least 10% of patients with type 1 diabetes at some point in their lives[5], with a prevalence that varies between 0.6%-16.4%, according to different studies[6-8]. The prevalence of celiac disease among children with type 1 diabetes is significantly higher than in non-diabetic children (in Western countries celiac disease affects around 1%-2% of the non-diabetic population).

In Italy, the prevalence of celiac disease in children with type 1 diabetes is around 7%[9,10], 3.6% of which at type 1 diabetes onset[9], at a younger age[10] and in boys[10]; moreover, according to a study by Salardi *et al*[11], the prevalence of celiac disease has significantly increased since 1994 (10.6% *vs* 6.6%, $P = 0.015$), probably due to changes in environmental factors, namely, eating habits and viral infections.

Less than 10% of patients with type 1 diabetes who develop celiac disease show gastrointestinal symptoms, while most of the children are either asymptomatic or only mildly symptomatic. Therefore, children affected by type 1 diabetes undergo screening for celiac disease. Usually, celiac autoantibodies are tested at the time of diabetes onset and yearly during follow-up, but debate exists about timing and frequency for screening[12,13]. When celiac antibodies are detected (ideally confirmed at least twice), it is mandatory to perform esophagogastroduodenoscopy with bowel biopsies to confirm diagnosis[14].

TREATMENT OF CELIAC DISEASE FOR PATIENTS WITH TYPE 1 DIABETES

The presence of mucosal atrophy is an indication to start a gluten-free diet (GFD), which is the standard therapy for celiac disease, avoiding all foods containing wheat, rye, barley and oats.

Patients affected by celiac disease must follow a strict GFD for their entire life to prevent acute (malabsorption, diarrhea, folate deficiency, failure to thrive, iron deficiency) and chronic (intestinal lymphoma, osteoporosis, autoimmune diseases, infertility, mortality) complications[12,15,16].

Gluten restriction added to a diabetic dietary regimen imposes practical limitations and leads to considerable restrictions in the lifestyle of a child or adolescent. Unfortunately, as a result, non-adherence to GFD among patients with type 1 diabetes and celiac disease is very common. A study by Valerio *et al*[17] found that only 59% of patients with type 1 diabetes and celiac disease were compliant to a strict GFD, while compliance in patients with celiac disease only is around 78%[18]. This is an important factor to consider when treating a child or adolescent with type 1 diabetes. It is well established that an accurate diet is one of the cornerstone of the management in patients with type 1 diabetes[19]. Combining a GFD may raise major challenges and even some doubts. Dietary intervention aims to achieve and maintain blood glucose and blood pressure in the normal range, to attain normal lipid profile, to achieve normal body weight[19]. Preserving a steady glycemic control is essential to reduce both micro and macrovascular complications of type 1 diabetes[20]. For this reason, it is important to give patients advice on carbohydrate amount, type and distribution throughout the day, and to educate them about carbohydrate counting. In this context, the choice of low glycemic index food may be important[21]. In this respect, a GFD could be an obstacle as many of the gluten-free foods have a high glycemic index. This might influence glycemic values, HbA1c, insulin requirement, lipid profile, and possibly the development of long-term diabetic complications. Moreover, GFD could modify both anthropometric measures, such as height, weight, body mass index (BMI), growth velocity, even if not all researchers agree on the final effects of GFD.

BODY MASS INDEX IN CHILDREN WITH TYPE 1 DIABETES AND CELIAC DISEASE

While, in patients with celiac disease alone, concern has been raised about gaining weight when on a GFD[22], recent data show normal growth patterns in children and adolescents with type 1 diabetes and celiac disease[23], with body mass index and height standard deviation scores only marginally but not significantly higher in the control (non-celiac) than the study group, and similar to subjects with celiac disease with good or fair/poor adherence to a GFD throughout the follow-up period. Among the reasons for increased BMI, the macronutrient composition of gluten-free foods, a high percentage of saturated fat and carbohydrates with high glycemic index, and a low percentage of proteins and fiber can be included.

After clearing gluten, as villous atrophy resolves, intestinal absorption is certainly improved, but an excessive weight gain may increase the risk of morbidity and may

lead to higher risk of cardiovascular disease[24] especially in type 1 diabetes patients. However, data on weight gain (and BMI increasing) in patients with celiac disease are inconsistent. Dickey *et al*[22] showed that nearly 80% of patients gained some weight after 2 years on GFD, and about 51% were even overweight or obese. On the contrary, a recent study reported a weight loss in obese or overweight patients while on GFD[25], with a similar improvement in screen- and symptom-detected celiac disease patients on a GFD.

GLYCEMIC CONTROL IN CHILDREN WITH TYPE 1 DIABETES AND CELIAC DISEASE

Regarding patients with type 1 diabetes and celiac disease, the most recent data show no difference between patients with and without celiac disease[23]. However, a link between a change in body mass index and a possible improvement of metabolic control remains controversial. Acerini *et al*[26] observed an improvement both in body mass index and in HbA1c, while Nóvoa Medina *et al*[27], who studied only type 1 diabetes patients with symptomatic celiac disease, did not find any effects on metabolic control or on height or weight.

Other studies evaluated the influence of a GFD on metabolic parameters, such as insulin dose, HbA1c, glucose excretion and hypoglycemic episodes. Saadah *et al*[28] observed that a GFD resulted in a significant improvement of growth and influenced diabetic control (more insulin in celiac disease patients when compared to baseline). Other authors[26,29] did not find any significant difference in insulin dose, HbA1c, 24 h urinary glucose excretion, or number of hypoglycemic episodes. Similar findings have been observed in adult patients with type 1 diabetes and celiac disease[30]. Abid *et al*[31] documented in type 1 diabetes children with celiac disease that a GFD showed short-term benefits by reducing gastrointestinal symptoms and, in particular, episodes of severe hypoglycemia, while there was no change in standard deviation score for height, weight, and BMI or the mean HbA1c before and after GFD. The mean insulin requirement significantly increased. More refined indexes of an altered or better metabolic control, like continuous glucose monitoring, glycemic variability indexes, and frequency of insulin dose changes are usually difficult to measure.

TYPE 1 DIABETES, CELIAC DISEASE AND MICRO OR MACROANGIOPATHIC COMPLICATIONS

Few studies have been published about this topic and almost all involved adult patients with type 1 and celiac disease. Bakker *et al*[32] collected HbA1c before celiac disease diagnosis, at diagnosis and the most recent together with the presence of nephropathy and retinopathy. An interesting finding was that diabetes patients with celiac disease had a lower prevalence of retinopathy when compared to controls (diabetes patients without celiac disease), whereas no difference in the prevalence of nephropathy was found, suggesting that a GFD possibly favorably affects the development of vascular complications in diabetes patients.

Similar findings have also been observed about macrovascular complications. Picarelli *et al*[33], evaluated whether the presence of celiac disease in a group of type 1 diabetes patients is associated with different expression of some hemostatic factors and with a different manifestation/progression of complications. The authors claim a potential protective role of celiac disease in the prothrombotic state of type 1 diabetes (celiac disease patients had significantly lower HbA1c, total cholesterol, triglycerides, factor Ⅷ antigen, factor Ⅶ coagulant activity, and prothrombin degradation fragments). In contrast, Pitocco *et al*[34] found that in type 1 diabetes patients with long duration of celiac disease, the carotid intima-media layer was thicker compared to diabetes patients without celiac disease.

However, if GFD seems to have a protective role in the appearance of micro- and macroangiopathic complications, the misdiagnosis of celiac disease in adult patients with type 1 diabetes is associated with a higher prevalence of retinopathy, nephropathy and peripheral neuropathy[35]. These findings raise the issue of regular celiac disease screening in order to detect type 1 diabetes patients at risk of developing celiac disease in a timely manner.

In this context, the case reported by Sildorf *et al*[36] of a 6-year-old boy who, after type 1 diagnosis, even without celiac disease, was started on a GFD, gradually suspending insulin therapy and remaining free of exogenous insulin after 20 mo seems very interesting. The GFD was reported to be safe and without side effects, and it is believed that the GFD acted to prolong the remission phase of diabetes.

TYPE 1 DIABETES, CELIAC DISEASE AND GLYCEMIC INDEX

As stated above, the most difficult factor to handle for a child/adolescent with type 1 diabetes and celiac disease is that most GFD foods have a high glycemic index. Indeed, in 2002 the American Society for Clinical Nutrition compared many foods regarding their glycemic index. What they discovered was that gluten-free foods have a higher glycemic index than gluten-containing equivalents. Since glycemic index represents a direct measure of carbohydrate absorption, it is obvious that high glycemic index foods determine a rise in rapid blood glucose values. Hyperglycemia causes an increase in free fatty acids that induce oxidative stress and promote atherosclerosis[37]. On the other hand, the subsequent rapid fall in glucose removal is associated with a sensation of hunger and excessive caloric intake[38]. Thus, a diet with low glycemic index is suggested either because of a lack of normal insulin response to high glycemic index foods in diabetes patients, or because of the aim of reducing micro and macrovascular complications[21,39]. Indeed, we have seen that GFD seems to have a protective role rather than a

deteriorating one[32,33], even in pediatric age[40]. The means by which the presence of celiac disease might prevent micro- and macrovascular complications of diabetes asks further investigations. Hypothetically, a greater dietary vigilance, an increased awareness of food intake and several consultations by a skilled dietitian might result in a better controlled carbohydrate intake and could lead to healthier eating habits. Finally, gluten free foods have a reduced content of many micronutrients: B and D vitamins, calcium, iron, magnesium and zinc. In particular, calcium content in a GFD should be appropriate, since an impairment of bone metabolism and structure has been found both in type 1 diabetes and celiac disease.

CONCLUSION

Hence, it is important to evaluate the impact of a GFD on metabolic control, growth and nutritional status in children with type 1 diabetes and celiac disease.

Since compliance with a strict GFD and a safe choice of food for diabetes is not easy, these patients require extra education and dietary intervention.

A specialized follow-up and dietary counseling are essential in the management of patients affected by both type 1 diabetes and celiac disease.

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