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REVIEW

Co-occurrence of type 1 diabetes mellitus and celiac disease

Amit Akirov, Orit Pinhas-Hamiel

Amit Akirov, Beilinson Campus, Rabin Medical Center, Petach-Tikva 49100, Israel
Amit Akirov, Orit Pinhas-Hamiel, Sackler School of Medicine, Tel-Aviv University, Tel Aviv 69978, Israel
Orit Pinhas-Hamiel, Pediatric Endocrine and Diabetes Unit, Safra Children's Hospital, Sheba Medical Center, Ramat-Gan 52621, Israel

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Correspondence to: Amit Akirov, MD, Beilinson Campus, Rabin Medical Center, 1 Kaplan Street, Petach-Tikva 49100, Israel. amit.akirov@gmail.com
Telephone: +972-3-524650760
Fax: +972-3-9221605

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Abstract

The co-occurrence of celiac disease (CD) and type 1 diabetes (T1DM) has been reported as 5-7 times more prevalent than CD alone. The clinical presentation and natural history of CD in patients with T1DM may vary considerably. Less than 10% of patients with T1DM and CD show gastrointestinal symptoms. Therefore, experts support screening for CD in T1DM patients, though there is no consensus as to the recommended frequency of screening. When stratified by time since CD diagnosis, longer follow-up and coexistence of CD are associated with significant increased risk of diabetic associated morbidity and mortality. Early CD diagnosis and treatment with a gluten-free diet are essential.

Key words: Type 1 diabetes mellitus; Celiac disease; Glycemic control; Gluten free diet; Pediatrics

Core tip: Increased prevalence rates of celiac disease (CD) are described among individuals with type 1 diabetes mellitus (T1DM). Specifically celiac disease is more prevalent in females with T1DM. Less than 10% of patients with T1DM and CD show gastrointestinal symptoms therefore screening is necessary. The significant increase of diabetic associated morbidity and mortality, emphasize the importance of early diagnosis of CD and appropriate treatment with gluten-free diet.

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INTRODUCTION

Celiac disease

Celiac disease (CD), previously known as celiac sprue, affects 0.6%-1.0% of the population worldwide, with wide geographic variation, for unknown reasons[1,2]. The autoimmune disorder is triggered in genetically

predisposed patients by gluten ingestion[1-4]. Symptoms of CD include malabsorption and malnutrition, vitamin deficiencies, iron deficiency anemia, failure to thrive, short stature, diarrhea, anorexia, constipation, vomiting, and abdominal distension. Other complications associated with untreated CD include osteoporosis, obstetric complications, and neurologic disorders, as well as enteropathy-associated T-cell lymphoma and adenocarcinoma of the jejunum[5,6]. However, several reports in the literature state that many cases of CD are asymptomatic or associated with mild symptoms[7-9]. Diagnosis of CD is based on intestinal biopsy and the presence of specific antibodies; however, most cases of CD remain undiagnosed[10,11]. Currently, the only effective treatment for CD is a lifelong gluten-free diet (GFD), which results in resolution or improvement for most individuals[12].

Epidemiology of T1DM and CD

The association between CD and T1DM was first described in the late 1960s[13]. Studies published during the last few years have demonstrated elevated prevalence rates of CD among individuals with T1DM: 4.4% in the United Kingdom, 3.7% in Israel, 4.8% in Greece, and 6.4% in Germany; and as high as 10.5% in Brazil and 11.1% in India[14-19].

The incidence of T1DM is rapidly increasing in children and adolescents, with a reported increase of 3% annually[20,21]. Similarly, a longitudinal study documented an increase in the prevalence of CD in the mid 1990s, from 3.3% to 10.6%, most probably due to changes in environmental factors[22].

CD is a female predominant disease, and is 2-3 times more common among females[23]. Although there is no gender difference in the prevalence rates of T1DM, CD is also more prevalent in females than in males with T1DM. The etiological risk factors for developing antibodies against the small bowel are thought to be different from those for T1DM[24-26].

Genetics

Genetic background plays a key role in the predisposition to CD, as suggested by higher prevalence among family members and higher concordance rates in monozygotic than dizygotic twins (over 80% compared with 11%)[27].

The human leukocyte antigen (HLA) plays a key role in the genetic predisposition to CD, as there is a strong association between both *HLA-DQ2* and *HLA-DQ8*, and between CD. The negative predictive value of HLA typing is high, as CD is extremely rare in patients carrying neither *DQ2* nor *DQ8* alleles[28,29].

An overlap in the genetic susceptibility conferred by *HLA-DQ2* is the basis for the increased prevalence of CD in patients with T1DM. Over 90% of those with CD express HLA-DR3/DQ2 haplotype, as well as 55% of those with T1DM, compared with less than 25% of the general population[30]. Bakker *et al*[31] confirmed the high prevalence of HLA-DQ2 haplotypes in patients with both T1DM and CD, and reported that HLA-DQ2 homozygosity confers the highest risk for CD among patients with CD. DQ2 has been cited by a number of studies as the major susceptibility factor for CD. *HLA-DQ8*, another important allele for CD, is considered a stronger susceptibility factor for T1DM. DQ8 heterozygosity is claimed to be the strongest risk factor for the development of T1DM[32,33]. Trynka *et al*[34] reported 57 independent CD association signals from 39 non-HLA genes that confer a predisposition to CD. However, although genetic predisposition is essential, it is not sufficient for the development of CD, as the pathogenesis of CD involves an external trigger, namely gluten.

SCREENING AND DIAGNOSIS

In the general population

According to the modified guidelines of the European Society of Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN)[10], testing for CD is recommended in children and adolescents with otherwise unexplained signs and symptoms suggestive of CD, and among asymptomatic children and adolescents with an increased risk for CD, such as patients with T1DM or first-degree relatives with CD.

Diagnosis of CD is based on the presence of villous atrophy and crypt hyperplasia by intestinal biopsy and the presence of antibodies against tissue transglutaminase (TTG) or endomysium (EMA). The diagnosis is confirmed by an antibody decline to a GFD. According to ESPGHAN guidelines, in patients with suspected CD and certain conditions (typical symptoms, high titer of TTG antibodies and predisposing HLA genotypes), there is no obligation to complete duodenal biopsy and histology[10].

Finally, potential CD, a term coined by Ferguson in the 1990s, refers to patients with positive CD-associated antibodies, but with normal, or almost normal, jejuna mucosa[35]. These patients usually have mild symptoms, if any, of CD. The number of patients diagnosed with potential CD is increasing, following the raised attention for CD and screening tests of high-risk populations[36]. Numerous studies in the general population demonstrate that CD is often only diagnosed after several years of CD related complaints[37-39]. Some reported that diagnosis of irritable bowel syndrome preceded the correct diagnosis of CD in many patients[40,41].

CD in T1DM patients

Less than 10% of patients with T1DM and CD show gastrointestinal symptoms[42]. Therefore, most professional societies recommend screening of patients with T1DM for CD. However, there is no consensus regarding the recommended screening tests and the frequency of screening[43].

Recommended screening test: Most guidelines support screening based on TTG IgA (confirmed by EMA), or TTG IgG in patients with IgA deficiency, because of its high sensitivity and specificity[44,45]. Most experts argue that in patients with CD-associated antibodies, it is mandatory to perform esophagoduodenoscopy with small bowel biopsies to confirm the diagnosis[10].

Timing and frequency of screening: Neither in the guidelines issued by ESPGHAN nor those issued by the National Institute for Health and Clinical Excellence, is the timing of screening specified. As for the frequency of screening, ESPGHAN guidelines recommend retesting at intervals, with no firm evidence, but opinion is every 2-3 years[10]. NICE guidelines state that the evidence is insufficient to make a recommendation regarding the frequency of screening for CD in patients with T1DM[10,46]. The International Society for Pediatric and Adolescent Diabetes recommends screening for CD at diagnosis of T1DM, every year in the first five years of follow-up, and less frequently in successive years[4,47,48].

Bakker *et al*[31] reported that almost 50% of T1DM patients diagnosed with CD in adulthood had CD related complaints for over 5 years prior to the diagnosis of CD. Furthermore, their findings demonstrated a bimodal distribution of the age of diagnosis of CD in patients with T1DM, with peak incidence rates at the ages of 10 and 45 years.

CLINICAL PRESENTATION OF CD IN PATIENTS WITH T1DM

CD diagnosis most often follows the diagnosis of T1DM, and only a minority of patients were diagnosed first with CD[7,31,49].

Age of onset

The mean age at onset of T1DM is younger in those with both T1DM and CD, than in those with only T1DM[25,50]. In an observational cohort study of 4379 people aged $\leqslant$ 18 years from Australia, the mean age at T1DM onset was 6.6 ± 4.0 years in those with T1DM and CD, compared with 8.4 ± 4.1 years in those without CD[51].

Signs and symptoms

The natural history of CD in patients with T1DM may vary considerably, as the diagnosis of CD can precede the diagnosis of T1DM, or be established at the onset of T1DM, during routine screening tests at follow-up. Accordingly, the presentation of CD varies greatly, from asymptomatic or mild symptoms to poor growth and considerable morbidity[7-9,44]. In individuals with diabetes, symptoms of CD may be divided into two main categories, those directly associated with CD and those related to the impact of CD on diabetes.

Signs and symptoms directly associated with CD

These include malabsorption and malnutrition, vitamin deficiencies, iron deficiency anemia, failure to thrive, short stature, diarrhea, anorexia, constipation, vomiting, and abdominal distension.

Growth in children with CD and T1DM compared to children with T1DM alone: As stated above, differences between reports may be due to whether CD diagnosis results from routine screening or is prompted from signs and symptoms.

Body weight was found to be significantly lower among children with T1DM with screening-identified CD compared to those with T1DM only; however, there was no difference in height[52]. Of 41951 children and adolescents surveyed in Germany, only 22273 (53%) had been screened for CD. Those with both T1DM and CD had a significantly lower weight standard deviation and height standard deviation score (SDS)[50]. In a subgroup of 183 patients, those with both diseases had significantly lower height and weight SDS after 5-year follow-up[53]. Previously, we demonstrated a higher prevalence of growth impairment among patients with both CD and T1DM, compared to patients with T1DM alone. Patients with CD were, on average, significantly shorter than their genetic target height potential, compared to patients with T1DM alone. Furthermore, poor adherence to GFD resulted in continuous growth impairment, compared to steady improvement among those with good adherence to a GFD[16]. Of note, patients with CD who do not improve their growth velocity after GFD should be evaluated for growth hormone deficiency secondary to autoimmune hypophysitis[54].

Signs related to the impact of CD on diabetes at diagnosis of CD

Glycemic control: Data remain inconsistent regarding glycemic control in patients with dual diagnosis of CD and T1DM. Data may differ based on the points of time HbA1c levels were assessed (at diagnosis *vs* at follow-up), whether diagnosis was based on routine screening or on symptoms, and in longitudinal studies whether adherence to GFD was assessed in parallel.

(1) HbA1c levels at diagnosis of CD. Malabsorption of nutrients may cause a reduction in HbA1c levels. In a controlled study in children mean age 10 years with T1DM duration of about 4 years, HbA1c levels at baseline did not differ significantly between patients with T1DM and CD, and between those with T1DM alone[55]. Yet, among adult T1DM patients who were newly diagnosed with CD, glycemic control was significantly worse than for those with T1DM alone, 8.2% *vs* 7.5%, $P = 0.05$[56]. The difference between these studies may reflect the impact of delayed diagnosis of CD.

(2) HbA1c levels at follow-up. In a controlled prospective 2-year follow-up study, mean HbA1c

levels did not differ significantly between patients with both T1DM and CD and between those with T1DM alone[57]. Similarly, in a large cohort from 297 centers in Germany and Austria, no statistically significant differences were found in mean HbA1c levels, between children with and without CD, mean age of 13.7 after 5 years of follow-up[50].

Acute events-hypoglycemic and diabetes keto-acidosis: CD is associated with mucosal changes that may interfere with the absorption of carbohydrates, even without leading to true malabsorption. An increased risk for symptomatic hypoglycemia was reported in the 6 mo before and after diagnosis of CD[58]. However, during long-term follow-up and under GFD, no differences were found in the numbers of severe hypoglycemic episodes[50]. There are no reports of increased risk of DKA episodes in individuals with both T1DM and CD[50].

Insulin requirements: One study reported significantly lower insulin requirements among patients with T1DM and CD than among those with T1DM alone[52]; yet the mean insulin requirement increased significantly from 0.88 to 1.1 units/kg per day after 12 mo GFD. In another study, there was no difference in insulin dosage per kilogram per day between patients with both T1DM and CD, mean CD duration of 3 years, and those without CD[59].

Other autoimmune diseases: Patients with CD are at increased risk for other autoimmune diseases, such as autoimmune thyroid disorders. Thyroid disorders have been reported to be an important risk factor for the development of CD among patients with T1DM[49,60].

COMPLICATIONS IN PATIENTS WITH T1DM AND CD

Complications may be divided into two main categories, those directly associated with CD and those related to the impact of CD on diabetes.

The long term complications associated with untreated CD include osteoporosis, obstetric complications, and neurologic disorders, as well as enteropathy-associated T-cell lymphoma and adenocarcinoma of the jejunum[2,6].

Diabetes associated complications in patients with CD

As for long-term complications among patients with T1DM and CD, the data are conflicting: some report that CD increases rates of complications[56], some show no difference, and others suggest lower incidence of complications[61]. These discrepancies may be due to differences in duration of undiagnosed CD.

Prevalence of complications in patients with T1DM and newly diagnosed CD

Among adults with T1DM duration of over 20 years, those with newly diagnosed CD had worse glycemic control and a significantly higher prevalence of retinopathy (58.3% *vs* 25%), nephropathy (41.6% *vs* 4.2%), and peripheral neuropathy (41.6% *vs* 16.6%)[56]. In contrast, Picarelli *et al*[61] reported significantly lower prevalence of nephropathy and retinopathy among adult T1DM aged about 50 years, with T1DM duration of about 18 years and newly diagnosed CD. The difference between these studies may be due to the unknown duration of undiagnosed CD, and to the difference in HbA1c levels between studies. In the latter, only those with HbA1c levels < 7.5% were included.

The prevalence of complications in patients with T1DM and CD: Long-term follow-up

A lower prevalence of retinopathy was reported in individuals with median durations of T1DM and CD of 27 and 3 years respectively, compared with controls (38.7% *vs* 67.4%). However, no difference in the prevalence of nephropathy was found between the groups[59]. The duration of CD was found to be correlated with the risk of diabetic retinopathy. When stratified by time since CD diagnosis, individuals with T1DM and CD were at a lower risk of retinopathy in the first 5 years after CD diagnosis, followed by a neutral risk in years 5 to 10. However, with longer follow-up, coexisting CD was a 2.83 increased risk factor for diabetic retinopathy at 10 to 15 years of follow-up, and a three-fold risk after 15 years of follow-up[62].

Patients with both T1DM and CD were reported to have more severe subclinical atherosclerosis than those presenting with only T1DM or CD. Among patients with both T1DM and CD, mean age of 39 years, mean T1DM duration of 18 years and CD duration of 8.5 years, carotid intima-media thickness was significantly greater in those with both T1DM and CD than in those with either T1DM or CD, suggesting that the association of these autoimmune diseases might accelerate the atherosclerotic process[63].

Finally, mortality in patients with both T1DM and CD was studied in 960 individuals aged 30 years, compared with 4608 with T1DM alone, matched for sex, age and disease duration. CD was not a risk factor for death in patients with T1DM during the first 5 years after CD diagnosis, but thereafter the hazard ratio for mortality increased as a function of follow-up time. Having a CD diagnosis for > 15 years was associated with a 2.80-fold increased risk of death in individuals with T1DM[64].

TREATMENT

The standard therapy for CD is GFD, which requires

avoiding wheat, rye, barley and oats. Patients with CD must follow this strict diet for their entire life. Delay in starting GFD increases the risk of osteoporosis, gastrointestinal malignancies, iron deficiency anemia, infertility, and other autoimmune disorders. Adherence to GFD augments the restrictions required by a diabetic dietary regimen.

GFD impact on glycemic control

Good glycemic control is essential to reduce the risks of T1DM related complications. However, many specially prepared gluten-free foods have high glycemic indices, and thus affect glucose levels, insulin requirements, lipid profiles and body mass indices (BMI). GFD may worsen glycemic control and can thus increase the difficulties of disease management for patients with T1DM and CD[42]. Numerous studies have evaluated the effect of CD and GFD on the metabolic control of patients with T1DM. Some reported better metabolic control with GFD among CD patients with T1DM[65,66]. Others did not show any change in HbA1c levels with GFD[67-72], and some reported worse glycemic control with GFD[73].

GFD impact on weight and height

Data on weight gain in patients with CD are inconsistent. Some studies report that treatment with GFD promotes a significant catch-up growth while others show no difference. The time of follow-up, age and stage of puberty of patients in different studies may explain the discrepancies. Twelve months after commencement of GFD, one study showed no statistically significant change in the SDS for height, weight and BMI of the 23 children assessed[74]. In a separate study, children with T1DM and CD had lower SDS for height and weight at CD diagnosis. After 2 years of follow-up, SDS was significantly increased for weight, and for height in prepubertal children[57].

Adherence to GFD

The compliance rates to GFD among patients with CD and T1DM is less than 60%, compared with about 80% among those with CD only[75]. The more severe problems of GFD adherence usually occur during adolescence[44].

QUALITY OF LIFE IN CHILDREN WITH T1DM

Families of children with both CD and T1DM report a higher burden than those affected by T1DM only. Similarly, health care providers perceived family burden to increase over time[76]. Yet, among children aged 8-18 years, no significant differences in quality of life were observed. However, parents of children with both CD and T1D did express greater concern about their children's social functioning. Adults (mean age 49 years) with both CD and T1DM scored lower in general health perception, social functioning and role limitation, as a result of physical health and emotional problems. In addition, concerns about diabetes related and social problems were significantly higher in those with both diagnoses[77].

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