Review

Celiac Disease and Type 1 Diabetes in Adults: Is This a High-Risk Group for Screening?

Emilia N. DeMelo MD [a], Charlotte McDonald MD [b], Fred Saibil MD [c], Margaret A. Marcon MD [d], Farid H. Mahmud MD, FRCP(C) [a,*]

[a] Division of Endocrinology, Hospital for Sick Children, Department of Pediatrics, University of Toronto, Toronto, Ontario, Canada
[b] Department of Medicine, Division of Endocrinology and Metabolism, St. Joseph's Health Care, University of Western Ontario, London, Ontario, Canada
[c] Division of Gastroenterology, Sunnybrook Health Sciences Centre, Department of Medicine, University of Toronto, Toronto, Ontario, Canada
[d] Division of Gastroenterology, Hepatology and Nutrition, Hospital for Sick Children, Department of Pediatrics, University of Toronto, Toronto, Ontario, Canada

ARTICLE INFO

ABSTRACT

The association between celiac disease (CD), an autoimmune condition involving intestinal inflammation related to gluten ingestion, and type 1 diabetes has long been recognized. CD prevalence rates 4 to 6 times greater in adults with type 1 diabetes than in the general population. Much of the existing literature focuses on important implications related to the impact of a gluten-free diet on short-term outcomes in metabolic control and quality of life. Canadian Diabetes Association guidelines recommend targeted CD screening in patients with type 1 diabetes who have classic symptoms, such as abdominal pain, bloating, diarrhea, unexplained weight loss or labile metabolic control; however, a significant proportion (40% to 60%) of patients may have mild or absent symptoms. Recent evidence suggests that adult patients with both conditions are at higher risk for diabetes microvascular comorbidities, increased mortality and impaired bone health if the CD is untreated. The purpose of this review is to describe the association between CD and type 1 diabetes and to summarize recent literature that evaluates risks in patients with both conditions.

© 2015 Canadian Diabetes Association

RÉSUMÉ

L'association entre la maladie cœliaque (MC), une maladie auto-immune impliquant une inflammation intestinale liée à l'ingestion de gluten, et le diabète de type 1 est reconnue depuis longtemps et la MC a des taux de prévalence 4 à 6 fois plus élevé chez les adultes atteints de diabète de type 1 que dans la population générale. Une grande partie de la littérature existante se concentre sur les implications importantes liées aux impacts des régimes sans gluten sur les bénéfices à court terme du contrôle métabolique et de la qualité de vie. Les lignes directrices de l'Association Canadienne du Diabète recommandent le dépistage ciblé de la MC chez les patients avec un diabète de type 1 qui ont des symptômes classiques, tels que des douleurs abdominales, des ballonnements, une diarrhée, une perte de poids inexpliquée, ou un faible contrôle métabolique; toutefois, une proportion importante (de 40% à 60%) des patients peut avoir des symptômes bénins ou absents. Des données récentes suggèrent que les patients adultes présentant ces deux conditions sont plus à risque de comorbidités avec des complications micro-vasculaires diabétiques, une augmentation de la mortalité et une santé osseuse altérée si la MC n'est pas traitée. Le but de cette revue est de décrire l'association entre la MC et le diabète de type 1 et de résumer la littérature récente qui évalue les risques chez les patients avec les deux conditions.

© 2015 Canadian Diabetes Association

Introduction

Dual diagnoses: type 1 diabetes and celiac disease

Celiac disease (CD) is routinely perceived to be more common in children with type 1 diabetes (1), but recent genetic and epidemiologic trends as well as screening data suggest that CD is highly prevalent in adults with type 1 diabetes as well. Type 1 diabetes

* Address for correspondence: Farid H. Mahmud, MD, FRCP(C), Hospital for Sick Children, 555 University Avenue, Toronto, Ontario M5G 1X8, Canada.
E-mail address: Farid.mahmud@sickkids.ca

and celiac disease are autoimmune diseases with shared genetic origins (2,3). Both are associated with the major histocompatibility-complex class II antigen DQ2, which is encoded by the alleles DQA1*501 and DQB1*201, thus providing a common genetic basis for disease expression (2,3). Recent shared non-HLA loci associated with CD and type 1 diabetes have also been described, including RGS1 on chromosome 1q31, IL18RAP on chromosome 2q12, TAGAP on chromosome 6q25, PTPN2 on chromosome 18p11, CTLA4 on chromosome 2q33, SH2B3 on chromosome 12q24, and a 32-bp insertion-deletion variant on chromosome 3p21 (2).

From an epidemiologic perspective, an increasing incidence of both autoimmune conditions has been reported. The incidence rate of CD has significantly increased by 2- to 3-fold over the past years in Western countries (4). In Canada, the prevalence of CD increased from 1.7% to 2.7% in the past 10 years (5), and in the United States, rates increased from 11.1 to 17.3 per 100 000 patient-years in the past 10 years, with peak age of onset observed in adulthood (45 to 85 years) (6). Similarly, a 20% increase in the prevalence of type 1 diabetes of 1.48 per 1000 people in 2001 to 1.93 per 1000 people in 2009 has been described in data from the United States (7). The North American annual increase incidence of type 1 diabetes is 5.3% as compared with Europe (3.2%) and Asia (4.0%), with Canada having the sixth highest rate of type 1 diabetes globally (8).

Across the age spectrum in patients with type 1 diabetes, 2 peaks in the incidence of CD have been described recently at 10 years and at 45 years of age. In adult patients with type 1 diabetes, 42% were diagnosed with CD 10 years after onset of type 1 diabetes (9). Moreover, CD serologic positivity in adult-onset type 1 diabetes was more likely to occur 15 years after diagnosis with diabetes (10). The prevalence of CD in adult patients with type 1 diabetes also varies across geographic locations. Larger studies from Europe report that the prevalence of biopsy-proven CD in adults with type 1 diabetes varies from 1.4% in the United Kingdom (11) to 5% in Ireland (12); other studies report similar values within this range (13—18). In North America, the prevalence of biopsy-proven CD in adult patients with type 1 diabetes ranges from 3.8% to 6.4% (19—22). In a community-based study in the United States that included patients of all ages, the prevalence of biopsy-proven CD in patients with type 1 diabetes was 6.8% in adults (22); similarly, a 5.1% prevalence rate was found in Australia (23) (Table 1).

Despite this increased prevalence of CD in patients with diabetes, challenges remain in establishing the diagnosis of CD in patients with type 1 diabetes because of the absence of symptoms. A higher proportion of patients with diabetes report subtle or no complaints at CD diagnosis (11—13,15—22), with the prevalence of asymptomatic patients with CD and type 1 diabetes ranging from 35.7% to 62.5% (11—13,16,17,19,20,22). Additionally, when present, symptoms are often attributed to diabetes-related neuropathy (24), leading to delays in diagnosis of CD; 48% of the adult patients had symptoms for more than 5 years before the diagnosis of CD, compared to 59% of pediatric patients' being diagnosed after fewer than 6 months of symptoms (9).

Consensus concerning CD screening in patients with diabetes varies across jurisdictions, particularly for differing age groups (24—28). In children, international guidelines recommend CD screening at diagnosis of type 1 diabetes and annually for 5 years (28), whereas other consensus-based guidelines, such as the Canadian Diabetes Association (27), differ by recommending serologic testing based solely on clinical symptoms, including recurring gastrointestinal symptoms, poor weight gain, anemia and unexplained frequent low blood sugar levels. For adults, the recommendations are less specific (24—26); the American College of Gastroenterology Guideline recommends CD screening in adults with type 1 diabetes if there are suggestive symptoms (26). Given the absent or minimal symptom profile of CD in adults with type 1

Table 1
Prevalence of celiac disease in adults with type 1 diabetes, based on existing studies

Location	Author	N	Age (years) (Mean)	Prevalence of CD in type 1 diabetes (%)
Europe				
Sweden	Sjoberg et al. 1998 (14)	848	46.1	1.8
Finland	Collin et al. 1989 (16)	195	17 to 62	4.1
United Kingdom	Page et al. 1994 (11)	767	22 to 80	1.4
Ireland	Cronin et al. 1997 (12)	101	15 to 59	5.0
Italy	Sategna-Guidetti et al. 1994 (18)	383	39.0	2.6
Spain	Vincuna Arregui et al. 2010 (13)	463	18 to 80	3.0
Turkey	Guvenc et al. 2002 (15)	100	15 to 60	4.0
Turkey	Aygun et al. 2005 (17)	122	Adults	2.5
North America				
USA	Talal et al. 1997 (20)	185	32.4 (median)	3.8
USA	Rensch et al. 1996 (21)	47	40.0	6.4
Mexico	Remes-Troche et al. 2008 (19)	84	28.9	5.9
Australia	Depczynski et al. 2007 (23)	98	Adults	5.1

diabetes, these medical practice guidelines may contribute to missed or delayed diagnosis of CD in this high-risk group.

The immunoglobulin A (IgA) antitissue transglutaminase (TTG) antibody, is the most sensitive and specific blood test for CD and remains the preferred single screening test for detection of CD; although other tests, such as the antiendomysial antibody and the antideamindated gliadin tests may also be used. Significant differences in screening rates have been reported in diabetes clinics on the basis of age, with one Ontario-based study reporting that 67% of pediatric sites actively screen for CD, whereas a study of North American adults with diabetes found that only 35.2% of sites engaged in routine CD screening, with 60.4% of them conducting screening according to symptoms and 42.9% screening at diagnosis of type 1 diabetes (29). It is important to note that in patients with type 1 diabetes and CD, lower CD serology titers have been described compared to non-diabetes CD patients (10,30). Although there may be some situations in which confirmatory duodenal biopsy is not performed (26), biopsy continues to be the gold standard for diagnosis of CD. Therefore, though the serology screening methods are typically highly specific and sensitive in the general population, in high-risk groups, such as those with type 1 diabetes, the combination of positive serology and positive duodenal biopsy is needed for diagnosis of CD (31), with the important caveat that patients should be consuming gluten during the diagnostic work-up. If patients have chosen to start a gluten-free diet (GFD) in advance of testing, it is important to be aware that there is controversy concerning what constitutes an adequate gluten challenge (32).

IgA deficiency, present in 1% to 3% of patients with CD, can result in false-negative serology, and anti-TTG IgG may be ordered in the known instance of IgA deficiency (26). Although testing for HLA-DQ2 and HLA-DQ8 are useful in the diagnosis of CD in the general population, this test is not recommended for the evaluation of patients with type 1 diabetes because most express an at-risk HLA CD haplotype (26).

A proposed scheme for the evaluation for CD of adult patients with type 1 diabetes on the basis of symptoms is presented in the Figure 1.

Bone health

Impaired bone health represents an important silent and insidious complication of CD in diabetes. CD has been associated with an increased risk of osteoporosis (33) and fractures in adults and impaired bone mineralization in children (34). A recent systematic review found a 30% increase in any fracture and a 69% increase in hip