

# Dietary gluten and the development of celiac disease and type I diabetes

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**Abstract:** The objective of this study was to perform a review of the present knowledge on the epidemiology and pathogenesis of the association between celiac disease (CD) and type 1 diabetes mellitus (T1DM). Results from this review show that the estimated prevalence rate of CD in T1DM ranges from 4% to 11.5%, which seems higher in children than in adults, while there is no sex predominance in the prevalence of CD in T1DM. On the basis of the previous literature, screening for CD should be considered at diabetes diagnosis in all subjects and again within 2 and 5 years after diagnosis, even in the absence of symptoms. The anti-islet antibodies detection test, instead, is not recommended in CD, just as in the general population, except for CD patients having a relative with T1DM. Both genes and environmental factors seem to play a role in this association. HLA-DQ2 has been found to be the most frequent allele in the patients with both CD and T1DM, while gluten may be considered the trigger that induces the production of autoantibodies and the development, in genetically predisposed individuals, of both diseases.

**Keywords:** diabetes, celiac disease, genetics, environmental, epidemiological

## Introduction

Celiac disease (CD) and type 1 diabetes mellitus (T1DM) are immune-mediated diseases that occur in genetically predisposed individuals. The causative agent of CD, “the gluten” is a protein contained in some cereals like wheat, which, once ingested and partially digested, induces an immunological response in the intestinal mucosa. On the contrary, it is still unknown what specific agent causes the destruction of the  $\beta$ -cells of the pancreas. Historically, it was believed that both diseases affected only children, but nowadays, it is known that CD can be diagnosed at any age, as can T1DM. In fact, although the latter remains the most common form of diabetes affecting children and adolescents, it can also be diagnosed during adulthood. CD may show a wide range of symptoms, or even be asymptomatic, and diagnosed only during screening programs. Similarly, T1DM can be diagnosed with the classic symptoms of new-onset chronic polydipsia, polyuria, and weight loss with hyperglycemia and ketonemia (or ketonuria), but it can also be discovered incidentally.<sup>1-4</sup>

We performed this review with the aim of discussing the present knowledge on the epidemiology and pathogenesis of the association between CD and T1DM. We searched PubMed for English-language articles published between 1900 and August 2015 for all the terms related to CD and T1DM. This search resulted in 1,319 papers, of which 293 were related reviews. Papers dealing with epidemiology and pathogenesis

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of the association of CD and T1DM were extracted, after which the most significant ones were used for this review.

## Epidemiology

The first reported case of T1DM and CD in the same patient was described by Payne<sup>5</sup> in 1954, with the association becoming evident in the early 1960s. Since then, some studies have confirmed the association, and nowadays, the estimated prevalence rate of CD in T1DM ranges from 4% to 11.5%.<sup>6–15</sup>

A recent pooled analysis, taking into account 27 studies with a total of 26,605 patients with T1DM, found a prevalence of biopsy-confirmed CD of 6.0% (95% confidence interval [CI] = 5.0%–6.9%). The prevalence was highest among children (6.2%) and lowest among adults (2.7%).<sup>16</sup> The heterogeneity of the prevalence of the association between CD and T1DM might be explained mostly by the age at screening, but can also be associated with the screening strategy and the tests used to diagnose CD. However, the prevalence of both diseases has increased over time; thus, the variability can also be related to the time the study was performed.<sup>17–20</sup>

Like other autoimmune diseases,<sup>21</sup> CD is more frequent in females than in males, with a ratio of around 2.5:1.<sup>22</sup> Conversely, T1DM is the only major organ-specific autoimmune disorder that does not show a strong female bias, while it is predominant in males, in particular, in countries with a high incidence.<sup>23</sup> The previous literature reported contradictory results between the sexes for the prevalence of CD in T1DM. The prevalence was higher in females in some studies,<sup>13,24</sup> higher in males in others,<sup>25,26</sup> and yet other studies reported no difference.<sup>27,28</sup> However, a meta-analysis published in 2014 described no sex predominance in the prevalence of CD in T1DM.<sup>16</sup>

A recent review<sup>29</sup> analyzed nine longitudinal cohort studies dealing with CD screening in T1DM children. The nine studies included altogether 11,157 children and adolescents with T1DM, of whom 587 had biopsy-reported CD (median follow-up 10 years). The pooled prevalence of CD was 5.1%. Only 41 cases (7%) were diagnosed with CD onset before T1DM, while CD was diagnosed in the first year from T1DM onset in 218 of 546 (40%) subjects. Thus, the important information derived from the Pham-Short et al<sup>29</sup> review is that, since 55% of cases were diagnosed within 2 years and 79% within 5 years from diabetes onset, screening for CD should be considered at diabetes diagnosis and again within 2 and 5 years after diagnosis. This datum is also confirmed by Larsson et al,<sup>25</sup> who suggested a screening for CD at the onset of T1DM, and annually for a minimum of at least 2 years.

The major limitation of the current data, however, is that almost all the screening studies deal with cohorts of T1DM children, and so the derived figures cannot be extrapolated for adults with T1DM. The reason to emphasize the notion of screening for CD in T1DM is that CD remains more often undiagnosed because of the low prevalence of gastrointestinal symptoms.<sup>30</sup> Apart from gastrointestinal symptoms, some studies have reported a poor control of glycemia level, which improves after initiation of the gluten-free diet (GFD).<sup>31</sup> However, based on the examined epidemiological studies on the prevalence of CD in T1DM, patients with T1DM should be routinely screened for CD.

No guideline indicates a specific timing for the screening because there is no longitudinal follow-up study on the onset of CD beyond 5 years of T1DM duration, despite the cast-iron certainty of the increased prevalence of CD in T1DM.

On the contrary, Kabbani et al<sup>32</sup> showed that CD patients on a GFD have a low risk of noninsulin-dependent diabetes mellitus, suggesting that the gluten contained in the diet may have a central role in causing the association of both diseases. No possibility exists that the onset of T1DM in CD could be less frequently detected, as it rarely continues nondiagnosed (as CD might in T1DM patients). In fact, the body's inability to produce insulin as a consequence of the autoimmune destruction of the  $\beta$ -cells in the pancreas causes some symptoms leading to a prompt T1DM diagnosis. T1DM diagnosis in patients with CD most often occurs in childhood, but it may also appear in adults in their late 30s and early 40s. However, there are no guidelines, and, at the moment, the anti-islet antibodies detection test is not recommended in CD, just as in the general population.<sup>33,34</sup> The only exception where the anti-islet antibody detection test is recommended is for CD patients having relatives with T1DM, because they are at risk.<sup>35</sup>

The reason for the diminished prevalence of T1DM after CD diagnosis is unclear, but it can be speculated that although the triggers for CD and T1DM are different, GFD and recovery of the intestinal mucosal barrier may play a role in inducing a sort of protection. Regarding this, recently it has been reported that the microbiota composition in the early gut is different between nonobese diabetic (NOD) mice that later in life become diabetic and non-diabetic. In particular, some Bacteroidetes are related to diabetes protection, whereas members of Firmicutes promote pathogenesis.<sup>36</sup>

The possibility of spontaneous normalization has been reported for elevated titer serum concentration of CD-related antibodies in 28% of 446 children with T1DM who chose not to follow a GFD.<sup>37</sup> Low titers of antitransglutaminase IgA

(TTG) antibodies (below eightfold the normal value) and anti-endomysial (EMA) negativity were the best predictors of spontaneous seroconversion. Moreover, no major events have been reported in EMAs and/or TTG-positive patients who, at diabetes diagnosis, chose not to follow the GFD, although they showed some nutritional deficiency at follow-up.<sup>38</sup>

## Pathogenesis

### Genetics

Genetics plays a role in both diseases, and overlap of genes may account for their co-occurrence.<sup>39</sup> Kumar et al<sup>40</sup> have recently summarized the results of several genetic studies that utilized the genome-wide association study technique to show genes and pathways involved in both the CD and T1DM phenotypes. In fact, the majority of CD patients express *HLA-DR3/DQ2* haplotype, and the same haplotype is present in 55% of those with T1DM and about 25% of the general population.<sup>41</sup> Homozygosity for *HLADQ2* confers the highest risk to develop CD, while homozygosity for *HLADQ8* confers the highest risk for T1DM.<sup>42</sup> *HLADQ2*, however, has been found to be the most frequent allele in the patients with both CD and T1DM.<sup>43–45</sup> The *HLADQ8* transdimer recognizes gluten and binds efficiently both gliadin peptides and also peptides derived from glutamic acid decarboxylase and islet cells antibody (IA-2).<sup>46</sup> As for CD, *HLA* genes are not the only genes contributing to T1DM.<sup>47</sup> A recent study reported that *KIR* genes play a role in the pathogenesis of the association between CD and T1DM.<sup>48</sup> Also, a recent genome-wide linkage and association analysis has shown the presence in CD of two out of three loci already known to be involved in regulating plasma glucose levels in T1DM.<sup>49</sup> CD and T1DM also share the IL-2/21 susceptibility locus, which is known to be associated with multiple autoimmune diseases.<sup>50–52</sup> In particular, all these studies highlight the role of IL-21, which is known to induce interferon- $\gamma$  production and regulate proliferation and survival of natural killer and CD8 T-cells in several autoimmune diseases. Genetics may also be involved in the clinical presentation of CD in T1DM. In fact, about 90% of T1DM patients at the time of diagnosis of CD have little or no gastrointestinal symptoms.<sup>53</sup> In the majority of cases, the CD diagnosis follows that of T1DM as a consequence of case-finding at diagnosis or follow-up; thus, CD is found at an early stage in patients with T1DM. On the contrary, there is a paucity of data on the onset of T1DM in patients with treated CD.<sup>54</sup> Genetically-induced lipid metabolism impairment often seen in CD patients with T1DM seems to be a consequence of T1DM and not related to the association. In fact, Tarnok et al<sup>55</sup> found low levels of n-3 long-chain poly-

unsaturated fatty acids in children with newly-diagnosed CD along with preexisting T1DM. The study suggests that CD on its own does not necessarily lead to impairment of essential fatty acid metabolism in plasma and supports the concept that T1DM has a significant impact on plasma fatty acid composition in children. Finally, an Italian study reported a 5.3% prevalence of immunoglobulin A deficiency in T1DM;<sup>56</sup> this was higher than that reported in CD.<sup>57</sup>

### Environment

It is believed that environmental factors, including nutrition, trigger the autoimmune process that precedes the development of T1DM. In children younger than 5 years of age, the early introduction of gluten has been involved in the etiology of T1DM with conflicting results.<sup>58,59</sup> Previous studies showed an increased risk of islet autoimmunity when food containing gluten<sup>60</sup> or any cereals<sup>61</sup> were introduced during the first 3 months of life in children at high risk for T1DM.

A substantially lower diabetes incidence was initially observed in NOD mice never exposed to a diet containing gluten (15%), compared to mice on the standard diet (64%).<sup>62</sup> However, in a successive study, the same authors surprisingly found that a gluten-enriched diet prevented diabetes in mice as efficiently as the GFD did.<sup>63</sup> The authors postulate two different mechanisms explaining the dually ambiguous response of NOD mice to gluten: activation of the immunity in the gut mucosa in the presence of low gluten doses and immunotolerance for very high doses.

Gluten might have a direct effect on pancreatic  $\beta$ -cells since it modulates the immune system and affects the pancreatic  $\beta$ -cells.<sup>64</sup> The 33-mer gliadin peptide (an immunogenic active peptide, made of residues 57–89 of  $\alpha 2$ -gliadin) and gluten (digested with digestive enzymes) increased in vitro, the long-term (24 hours), but not the short-term (30 minutes), insulin secretion via the closure of the ATP-sensitive K-channels. In vivo, NOD mice, injected with gliadin digest, were heavier as adults, probably reflecting the higher insulin secretion from the islets.<sup>65</sup>  $\beta$ -cell stress contributes to diabetes onset by increasing antigen expression, whereas prophylactic insulin treatment induces a reduction of diabetes incidence in diabetes-prone animals.<sup>66</sup> Some studies highlight the role of microbiota in degrading the toxic gluten proteins and/or regulating immunotolerance to gluten.<sup>67–69</sup>

It has also been shown that bacteria present in the gut may hydrolyze dietary gluten.<sup>70</sup> Thus, it can be speculated that a defective/altered microbiome may cause loss of immunotolerance and the onset, in genetically susceptible individuals, of both CD and T1DM.

Finally, viral infections have been suggested to play a role in triggering many autoimmune conditions, including CD and T1DM. The evidence is both epidemiologic and genetic. The *Toll-like receptors (TLR) 7* and *8* genes, encoding for the innate receptors for single-stranded viral RNA and related to the antiviral responses,<sup>71</sup> have been found to be associated with CD.<sup>72</sup> Similarly, the *TLR3* and *TLR4* genes, which play an important role in the innate immune response triggered by viral infection, are responsible for the development of both T1DM and CD.<sup>42,73,74</sup>

## Conclusion

In conclusion, in the absence of gastrointestinal symptoms, and/or growth failure and/or iron deficiency, CD blood tests should be performed at T1DM diagnosis and routinely repeated within 5 years from diagnosis, even in the absence of gastrointestinal symptoms. Conversely, the anti-islet antibody detection test is recommended for a CD patient having a relative with T1DM, as he/she is considered to be at risk. *HLADQ2* has been found to be the most frequent allele in patients with both CD and T1DM, but several others genes seem to be related to both diseases. Gluten, in the case of the association of CD and T1DM, may be considered the trigger that induces the production of autoantibodies and the development, in genetically predisposed individuals, of both diseases.

## Disclosure

The authors report no conflicts of interest in this work.

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