Introduction

The association between insulin-dependent diabetes mellitus (IDDM) and coeliac disease (CD) has been known for a long time (1) in both adults and children. It may be hypothesized that the association between CD and diabetes depends on a common genetic substrate, as both diseases share the same HLA (DR3/DR4, DQ2/DQ8). This interpretation does not explain why, in a vast majority of association cases, CD diagnosis comes after that of diabetes; why most of these patients show an atypical clinical pattern for CD characterised by very mild (2) and usually extraintestinal symptoms and why only around 10% of them are identified through classic symptoms (3). A possible interpretation of these data is that undiagnosed CD, in a subject who is not, therefore, on a gluten-free diet, is a predisposing factor for diabetes (4). Since atypical CD can easily be recognised by determining the antigliadin (AGA), antiendomysium (AEA) (5,6) and anti-transglutaminase (tTG) (7) antibodies, the above-mentioned serological tests have been applied to the CD screening of subjects affected by IDDM (8,9,10,11).

Epidemiology

A possible association between IDDM and CD was first reported in 1951 (12) when an increased incidence of diabetes was found among the first-degree relatives of coeliac patients. Further studies have confirmed this association and have reported high prevalence rates, ranging from 1 to 16.4-20% in the paediatric and adult diabetic population, depending on geographical areas, different case studies and screening tests used (13,14) (Table 1).

<table>
<thead>
<tr>
<th>Author</th>
<th>Patients</th>
<th>CD prevalence (%)</th>
<th>Screening tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boudraa et al. 1996</td>
<td>116</td>
<td>16.4</td>
<td>AGA and EMA</td>
</tr>
<tr>
<td>Ertekin et al. 2006</td>
<td>74</td>
<td>13.5</td>
<td>tTG and Biopsy</td>
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<tr>
<td>Hansen et al. 2006</td>
<td>269</td>
<td>12.3</td>
<td>tTG and EMA</td>
</tr>
<tr>
<td>Nimri et al. 2006</td>
<td>42</td>
<td>12</td>
<td>tTG and EMA</td>
</tr>
<tr>
<td>Araujo et al. 2006</td>
<td>354</td>
<td>10.5</td>
<td>AGA and EMA</td>
</tr>
<tr>
<td>Ashabani et al. 2003</td>
<td>234</td>
<td>10.3</td>
<td>AGA, tTG, ARA, EMA</td>
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<tr>
<td>Serkon et al. 2002</td>
<td>100</td>
<td>6</td>
<td>EMA</td>
</tr>
<tr>
<td>Zbikowska- B. et al.2006</td>
<td>446</td>
<td>5.1</td>
<td>EMA</td>
</tr>
<tr>
<td>Sanchez-A. et al. 2005</td>
<td>281</td>
<td>3.9</td>
<td>AGA and EMA</td>
</tr>
<tr>
<td>Bonguerra et al. 2005</td>
<td>348</td>
<td>2.3</td>
<td>tTG and EMA</td>
</tr>
</tbody>
</table>

Pathogenesis

Several studies carried out on different populations have focused on the association between CD and IDDM. The result was a high prevalence of coeliac disease and a greater predisposition to developing this disease among patients with early onset diabetes. The opposite is also true: coeliac patients can develop diabetes over time, especially if untreated (24).
The two diseases share a common genetic substrate represented by the same HLA (DR3/DR4, DQ2/DQ8). The genetic predisposition is also a risk for the relatives of coeliac and diabetic subjects. The results of a recent study comparing the genotypic data of 130 diabetic children with CD and 245 children only affected by IDDM show that the risk of developing coeliac disease in children with type-1 diabetes is significantly influenced by both the presence of HLA-DQA1*05/DQB1*02 and another gene of the Major Histocompatibility Complex, TNF-308A.

Similarity of genetic background is not the only feature that the two diseases have in common. A causal role of gluten intolerance has been hypothesised in the development of an autoimmune reaction against the pancreas. Gluten is, therefore, regarded as one of the environmental factors capable of increasing the risk of developing diabetes. This statement is corroborated by several observations:

- anti-pancreas antibodies, if present in coeliac patients, tend to disappear after a gluten-free diet is introduced.
- geographical regions (e.g. Japan, Korea, Polynesia), characterised by a low consumption of wheat flour, have a lower incidence of diabetes.
- in diabetic subjects, anti-tTG antibodies turn positive at a rather late stage, which is evidence of gluten intolerance onset.

The identification of an autoimmune response against tTG in the mucosa of diabetic subjects is, therefore, a risk factor for the development of autoimmune diseases, such as coeliac disease.

**IDDM and CD: screening tests**

The serological tests available for the screening of CD in patients with IDDM include anti-tTG, EMA, AGA (both IgA and IgG classes for all). In a recent publication, the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition has suggested the anti-tTG antibody assay, associated with intestinal biopsy, as the elective test for the initial CD screening stages. However, the presence of anti-endomysium antibodies in patients with a recent IDDM diagnosis may be a sign of a high probability of coeliac disease, as these antibodies appear to be correlated to the degree of mucosal damage. Furthermore, a recent article has confirmed the prevalence of CD in patients affected by IDDM, obtaining a result of 6.4% in a screening exclusively based on EMA antibody assay. The same authors obtained a decisively higher figure (13.8%) by including EMA IgG antibody assay in the screening, thereby highlighting the importance of these isotopes for CD diagnosis.

**Conclusions**

Ever since serological screening became a widely used tool in clinical practice, many CD cases have been diagnosed within one year of IDDM onset, even if sometimes CD antibodies become positive only at a later stage. It is, therefore, advisable for all subjects with IDDM, irrespective of the symptoms presented, to be submitted to the monitoring of serological markers at least once a year. The treatment of CD has a favourable effect on diabetes because it contributes to improving metabolic control and, possibly, reducing the insulin requirement, as well as preventing possible “silent” complications such as anaemia and osteoporosis.

**Bibliography**

Coeliac Disease and Insulin-dependent Diabetes


