Coeliac Disease and.....

- Anaemia, Iron Deficiency
- Autoimmune disorders
- Heart conditions
- Insulin-dependent diabetes mellitus
- Bone & calcium disorder
- The liver
- Malignancy
- Neuro-Psychiatric Disorders
- Fertility
Anaemia, Iron Deficiency and Coeliac Disease

Introduction
Anaemia and/or iron deficiency is a frequent laboratory finding in subjects with coeliac disease (CD). Many studies have clearly shown that the clinical presentation of CD is very often heterogeneous, as this condition is usually found with a low-grade intensity illness or atypically with extraintestinal symptoms. In some of these cases, an abnormal haematological pattern may be the only presenting finding of gluten-sensitive enteropathy.

Epidemiology
Anaemia secondary to iron, folic acid and/or vitamin B(12) malabsorption is the most common complication of CD and most patients present with it at the time of diagnosis. Many studies have reported a prevalence of anaemia in 12-69% of the subjects with a recent diagnosis of coeliac disease. Furthermore, CD is often diagnosed in patients affected by anaemia and, in particular, it is the subclinical form of CD that turns out to be a frequent cause of anaemia and/or iron deficiency (Table 1).

<table>
<thead>
<tr>
<th>Author</th>
<th>Patients with anaemia</th>
<th>CD prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unsworth et al 2000</td>
<td>200</td>
<td>6.6</td>
</tr>
<tr>
<td>Haslam et al. 2001</td>
<td>216</td>
<td>2.3</td>
</tr>
<tr>
<td>Annibale et al. 2001</td>
<td>190</td>
<td>13.7</td>
</tr>
<tr>
<td>Howard et al. 2002</td>
<td>258</td>
<td>10.9</td>
</tr>
<tr>
<td>Ransford et al.</td>
<td>484</td>
<td>3.5</td>
</tr>
<tr>
<td>Grisolano et al. 2004</td>
<td>103</td>
<td>8.7</td>
</tr>
<tr>
<td>Mandal et al. 2004</td>
<td>504</td>
<td>1.8</td>
</tr>
<tr>
<td>Karnam et al. 2004</td>
<td>105</td>
<td>2.8</td>
</tr>
<tr>
<td>Kalayci et al. 2005</td>
<td>135</td>
<td>4.4</td>
</tr>
<tr>
<td>Hershko et al. 2005</td>
<td>150</td>
<td>5</td>
</tr>
</tbody>
</table>

Anaemia and/or iron deficiency and CD: the laboratory
In both classic and subclinical forms of CD, anaemia is usually mild-moderate and hypochromic-microcytic: a reduction of the mean corpuscular haemoglobin content (IMCHC) is associated with a decrease in the mean red cell volume (MCV). These findings are often associated with low serum bioavailable iron levels (iron deficiency) and reduced stored iron (serum ferritin and transferrin) (Table 2). A recent study has shown that serum soluble transferrin receptor (sTfR) and ferritin levels are a useful parameter for CD diagnosis in children affected by anaemia and/or refractory iron deficiency.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haemoglobin</td>
<td>Decreased</td>
</tr>
<tr>
<td>Mean corpuscular volume</td>
<td>Decreased</td>
</tr>
<tr>
<td>Red cell distribution width (%)</td>
<td>Increased</td>
</tr>
<tr>
<td>Erythrocyte protoporphyrin (pmol/l)</td>
<td>Increased</td>
</tr>
<tr>
<td>Blood Iron (mgr/dl)</td>
<td>Decreased</td>
</tr>
<tr>
<td>Total iron-binding capacity (mg/dl)</td>
<td>Increased</td>
</tr>
<tr>
<td>Serum ferritin (mcg/l)</td>
<td>Decreased</td>
</tr>
</tbody>
</table>
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Pathogenesis

The pathogenesis of iron deficiency in patients with CD is not yet completely understood and is likely to be multifactorial\(^1\)\(^,\)\(^3\)\(^,\)\(^23\). Three main mechanisms have been hypothesized:

1. Decreased oral iron intake caused by reduced food intake. This phenomenon is common in patients with typical forms of CD (usually affecting children during the first years of life) where anorexia and vomiting are the prevalent symptoms.
2. Iron malabsorption, which can be caused by a reduction in the available absorptive surface or by an alteration of the small intestinal mucosa brush border.
3. Increased iron losses within the small intestine. This phenomenon could be related to either the rapid enterocyte turnover rate which causes alteration of the epithelial-cell barrier, or the intestinal microerosions resulting from the chronic inflammation.

Conclusions

Iron deficiency with or without anaemia is a very frequent feature in patients with CD. In some cases (e.g. atypical or monosymptomatic CD) it is the only presenting complaint. The widespread use in clinical practice of reliable serological screening tests, such as IgA and IgG classes antitransglutaminase (tTG) and antiendomysium (EMA) antibodies, have permitted identification of atypical forms of CD and hence the diagnosis of a gluten-sensitive enteropathy in subjects with isolated anaemia and/or iron deficiency. In all these cases, the full recovery of the small intestinal mucosa following the adoption of a gluten-free diet, allows the haematological parameters to become normal\(^13\). The above-mentioned data confirm that CD serological markers should be checked in all subjects affected by unexplained iron-deficient anaemia, especially if this condition does not respond to oral iron therapy.

Essential Bibliography

17. AK Mandal, I Mehdi, SK Munshi, TC Lo. Value of routine duodenal biopsy in diagnosing celiac disease in
Coeliac Disease and....


Coeliac disease and autoimmune disorders

Introduction
Among the numerous conditions associated with coeliac disease (CD), an important role is played by autoimmune diseases. These disorders (in particular type-1 diabetes mellitus\(^1\) and autoimmune thyroid diseases\(^2,3\), but also Sjögren’s syndrome\(^4\) and IgA deficiency syndrome) have long been known to have an increased prevalence among coeliac subjects. Similarly, coeliac disease (usually undiagnosed) has a high prevalence among subjects with autoimmune diseases. Interestingly, the prevalence of CD, without gastroenterological symptoms, significantly increases whenever several autoimmune diseases are associated in the same patient\(^5,6\), and this is true not only in subjects affected by autoimmune diseases, but also in their first-degree relatives\(^15\). The association between autoimmune disorders and coeliac disease is usually ascribed to their sharing predisposing genetic factors. This genetic susceptibility mainly seems to affect the HLA region of chromosome 6. Moreover, there is abundant evidence leading to think that the spectrum of gluten-dependent autoimmunity is decisively wider than it was thought to date and that in coeliac subjects the onset of autoimmune manifestations, besides enteropathy, can also depend on gluten intake.

Table 1 - Autoimmune disease with HLA overlapping with CD

<table>
<thead>
<tr>
<th>Autoimmune Disease</th>
<th>HLA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dermatitis herpetiformis</td>
<td>DR3/DQ2 &amp; DR4/DQ8</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>DQ2/DQ8</td>
</tr>
<tr>
<td>Thyroid diseases</td>
<td>DQ2</td>
</tr>
<tr>
<td>Selective IgA deficiency</td>
<td>DR3-DR7/DQ2</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>DR4/DQ2 &amp; DR7/DQ2</td>
</tr>
<tr>
<td>Sjögren’s syndrome</td>
<td>DR3/DQ2</td>
</tr>
<tr>
<td>Addison’s disease</td>
<td>DR3/DQ2 &amp; DR4/DQ8</td>
</tr>
<tr>
<td>Spondyloarthropathies</td>
<td>DR4</td>
</tr>
<tr>
<td>Chronic autoimmune hepatitis</td>
<td>DR3/DQ2</td>
</tr>
<tr>
<td>Dilated cardiomyopathy</td>
<td>DR4 predisposing &amp; DR3 protective</td>
</tr>
<tr>
<td>Systemic Lupus Erythematosus</td>
<td>DR3</td>
</tr>
</tbody>
</table>

Epidemiology
As early as the 70s, autoimmune diseases\(^7\) had been identified in 19% of a group of 57 coeliac patients. Over the years, further investigations showed a “higher-than-expected” prevalence of autoimmune disorders in both coeliac children and adults. An extensive Italian multicentre study has demonstrated that the prevalence of autoimmune diseases in coeliac adolescents is much higher than in the general peer population (13.6% vs. 5.2%, p <0.000001), but it is undoubtedly more interesting to underline that prevalence depends on age at diagnosis, i.e. on the duration of gluten exposure\(^8\). Further studies have also shown a similarly high CD prevalence in subjects with autoimmune diseases (Table 2)\(^9-14\).
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Table 2. CD prevalence in autoimmune diseases.

<table>
<thead>
<tr>
<th>Author</th>
<th>Autoimmune disease</th>
<th>Patients (n°)</th>
<th>Patients with CD (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mysliwiec M. et al. 2006(9)</td>
<td>Type-1 diabetes</td>
<td>223</td>
<td>9.4</td>
</tr>
<tr>
<td>O’Leary C. et al. 2002(10)</td>
<td>Addison’s disease</td>
<td>41</td>
<td>12.2</td>
</tr>
<tr>
<td>Szodoray P. et al. 2004(11)</td>
<td>Sjögren’s syndrome</td>
<td>111</td>
<td>4.5</td>
</tr>
<tr>
<td>Larizza D. et al. 2001(12)</td>
<td>Thyroiditis</td>
<td>90</td>
<td>7.8</td>
</tr>
<tr>
<td>Prati D. et al. 2002(13)</td>
<td>Dilated cardiomyopathy</td>
<td>642</td>
<td>1.9</td>
</tr>
<tr>
<td>Collin P. et al. 2002(14)</td>
<td>Berger’s disease</td>
<td>223</td>
<td>3.6</td>
</tr>
<tr>
<td>Villalta D. et al. 2005(15)</td>
<td>Autoimmune hepatitis</td>
<td>47</td>
<td>6.4</td>
</tr>
<tr>
<td>De Bem RS et al. 2006(16)</td>
<td>Dilated cardiopathy</td>
<td>74</td>
<td>2.6-6.7</td>
</tr>
</tbody>
</table>

Risk of autoimmune diseases in CD patients’ first-degree relatives.

A study among first-degree relatives of subjects with CD\(^{(17)}\) has observed a prevalence of autoimmune diseases at least six times higher than the prevalence among first-degree relatives of healthy subjects, and in particular that the risk is closely correlated with age. A subset, including first-degree relatives of CD patients, equally affected by silent CD, presented with a significantly higher prevalence of autoimmune diseases in comparison with first-degree relatives not affected by CD, with an OR value of 6.3\(^{(17)}\). The authors concluded that the first-degree relatives of subjects with gluten-sensitive enteropathy present with an increased risk of developing autoimmune diseases, probably correlated with an undiagnosed and, therefore, untreated coeliac disease.

Pathogenesis

The pathogenetic mechanism underlying the association between gluten-sensitive enteropathy and autoimmune diseases has not been fully clarified yet; genetic predisposition, immunological mechanisms and environmental factors (because of its vast surface in contact with the environment, the bowel is the first entrance point for any environmental “triggers” of autoimmune diseases) are all involved in the etiopathogenesis of both conditions. In earlier times, it was suggested the possibility of an accumulation of immune complexes\(^{(18)}\), but this was not confirmed by further studies. More recently, the evidence of IgA deposits in the extracellular transglutaminase (TG2) of the liver, muscle and lymphatic ganglia shows that this enzyme is accessible to the autoantibodies synthesized in the intestinal mucosa\(^{(19)}\). T-lymphocytes specifically directed against transglutaminase have resulted to be able to escape thymic control and trigger a specific and rapid immunological reaction at any site of the organism, if large concentrations of epitopes are present\(^{(20)}\). Severe intestinal disorders in coeliac patients (related to the liver, the heart, the nervous system, etc.) may be correlated with the presence of in situ autoantibodies. Furthermore, some studies suggest a causal relation between gluten-intake and onset of autoimmune disorders. The risk of developing autoimmune diseases is significantly correlated with the duration of gluten exposure\(^{(8)}\) and, thus, age at diagnosis (Graph 1).

Graph 1.

Risk of autoimmune diseases correlated with duration of gluten exposure.
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Conclusions

All the above emphasizes the importance of a proper anamnestic and clinical evaluation of the patient with autoimmune disease with the aim of presenting an early and appropriate diagnosis. Considering the high prevalence of autoimmune diseases in patients with gluten-sensitive enteropathy, early CD diagnosis becomes essential. Likewise, treating patients with a gluten-free diet is fundamental to achieve clinical improvements, at least in the case of those diseases for which the effectiveness of this approach has been demonstrated.

Bibliography

Coeliac disease and heart conditions

Introduction

In addition to the better known clinical manifestations suggesting gluten intolerance, recently new disease associations have been reported, such as cardiovascular diseases. The impact of these new associations on coeliac disease (CD) is surely lower than that of other endocrine diseases, anaemia and myeloproliferative disorders. In the literature, references to this subject are few and case studies are often limited. However, these diseases are not negligible and in some cases treatment with a gluten-free diet can be a suitable way to prevent disease development or improve symptoms.

Clinical and epidemiological aspects

With regard to the study of this association, the studies published on the risk of CD in subjects affected by dilated cardiomyopathy (dCMP) are indeed more numerous: a prevalence of gluten-sensitive enteropathy of 5.7% has been estimated in patients affected by this cardiovascular disease\(^1\,^2\). In an important study CD screening was carried out on 52 subjects with idiopathic cardiomyopathy who were accurately examined by coronarography and endomyocardial biopsy\(^1\); in 3 out of 52 patients - i.e. in a rather high percentage (approx. 6%) - villous atrophy was observed.

Later, a retrospective study\(^3\) conducted on 238 patients with dCMP, their 28 relatives with initial electrocardiographic or echocardiographic changes and 393 healthy relatives showed positive results to anti-tTG antibody assay for 6 subjects with dCMP; all 6 of them resulted to be positive for HLA DQ2-DQ8 and intestinal biopsy showed the typical lesions of coeliac disease in each of them. Furthermore, 7% of the 28 relatives with instrumental changes suggesting dCMP and only 0.7% of healthy relatives were positive to CD-specific antibodies. Thus, the results show that genetically-determined gluten intolerance can be an important factor in the autoimmune genesis of idiopathic dCMP, like it has been demonstrated for other diseases. Furthermore, considering the high CD prevalence among relatives affected by idiopathic dCMP changes, it may be inferred that serological screening can be useful to prevent the development of heart disease.

An Italian study\(^4\) surveyed 187 patients, 110 with heart failure and 77 with arrhythmias, for whom a diagnosis of autoimmune myocarditis had been presented. 4.4% of them were positive to antiendomysium and anti-transglutaminase antibodies, a statistically significant finding if compared with 0.6% of healthy controls. Five out of nine subjects with a new CD diagnosis, and affected by heart failure, were treated with a gluten-free diet associated with an immunosuppressive therapy; the gluten-free diet was the only treatment for the remaining 4 coeliac patients with autoimmune myocarditis and extrasystoles. The result was an evident clinical cardiovascular improvement and a negative result at the antibody assay for CD in all the nine patients after an 8-12 month treatment. A further recent study\(^5\) has assessed the prevalence of CD in 74 Brazilian patients affected by severe dilated cardiopathy: 2.63% of the subjects resulted to be positive to antiendomysium IgA antibodies, while as many as 5 examined patients (6.75%) were serologically positive to anti-tTG IgA antibodies.

As regards the association between pericarditis and coeliac disease, a recent study on 26 children affected by gluten-sensitive enteropathy\(^6\) demonstrated pericardial effusion in 50% of the examined subjects. Pericardial effusion was limited, asymptomatic and instrumentally detectable. In coeliac children presenting with this abnormality, a higher value of antiendomysium antibodies and a lower amount of selenium and iron were observed in comparison with children without effusion. Conversely, the ECG, chest radiography and other haematocchemical tests were very similar for both groups studied. In this case, too, an immunological cause was suggested to explain the association of the two diseases.

Another recent Italian study\(^7\), conducted on 642 patients on waiting list for heart transplant, found that 1.9% of these were positive to EMA antibodies (compared with 0.35% observed in 720 healthy controls); furthermore, 2.2% (compared with 1.6% among the remaining patients on the list for transplant) was the percentage of patients who were positive to the same antibodies among 275 patients of the same group, who however presented with dilated cardiomyopathy.

Moreover, in earlier times other studies concerning the association between latent CD and
cardiovascular diseases described cases of ventricular hyperkinetic arrhythmias related to a Q-T prolongation due to electrolytic disturbances, caused by villous atrophy, in subjects with gluten-sensitive enteropathy without gastrointestinal symptoms.

Another study is particularly interesting in this regard, since it identifies Q-T prolongation in one third of the coeliac patients studied, in comparison with no patients among subjects with chronic pancreatitis and intestinal disorders. In patients affected by CD an inverse relationship has been found between Q-T prolongation and blood potassium, hence the recommendation to supplement the diet therapy with potassium administration.

Finally, in 1976, upon studying the mortality rate among coeliacs, it was observed that mortality due to ischemic cardiopathy and stroke was 40% lower than in the general population, thereby hypothesizing a protective action by coeliac disease against the above-mentioned conditions, maybe because of the low cholesterol, triglyceride and fibrinogen levels characterising this disease. Another more recent study carried out on 3790 coeliac patients has confirmed a reduction in the risk of hypertension and hypercholesterolaemia and showed a lower risk of myocardial infarction; however, a slight increase in the risk of stroke was also observed. All these findings still require confirmation by other authors.

**Pathogenesis**

In order to explain this association, the autoimmune pathogenetic hypothesis appears to be the most convincing: in some patients with idiopathic dCMP and their relatives, the presence of autoantibodies directed against the heart has been identified and, some subjects present with the same histocompatibility antigens observable in disorders having a confirmed autoimmune pathogenesis. A further hypothesis is for the cardiac damage to have been caused by an autoimmune mechanism triggered by gliadin, as already demonstrated for other disorders associated with coeliac disease. Furthermore, the favourable effect of a gluten-free diet shows that the improvement in cardiac function may be due to an enhanced absorption of nutrients and oligoelements playing a beneficial role on myocardial contractility and electrical stability, as well as cardiovascular drug absorption. In these subjects, this is compromised by both villous atrophy, typical of CD, and protein-losing enteropathy, secondary to venous stasis, which is observable in the advanced stage of idiopathic dCMP. Furthermore, villous atrophy observed in coeliac disease can hinder the absorption of several nutrients such as thiamin, riboflavin, magnesium, calcium, selenium, carnitine, etc., which are active in myocardial metabolism. In particular, carnitine is an important carrier for the transport of acylc groups inside the mitochondria, where β-oxidation takes place; this substance can be detected in serum, skeletal muscles and heart tissue. An increment in carnitine levels can be effective for cardiac performance, as some authors have already observed in patients affected by dCMP and CD treated with a gluten-free diet.

**Conclusions**

In terms of statistical incidence, cardiovascular conditions play a secondary role in coeliac disease in comparison with endocrine and connective tissue diseases. However, in the light of the clinical and epidemiological observations described above, it is evident how these disorders can cause considerable complications in subjects affected by gluten-sensitive enteropathy. It is, therefore, reasonable to regard CD screening as a suitable diagnostic tool in subjects affected by cardiovascular diseases, given the evident favourable effect caused by a gluten-free diet on myocardial performance. Furthermore, considering the high prevalence of coeliac disease among the relatives of patients with dCMP, a serological screening can be all the more useful to prevent the development of heart disease, before this presents itself clinically.
Essential bibliography

**Insulin-dependent diabetes mellitus and coeliac disease**

**Introduction**

The association between insulin-dependent diabetes mellitus (IDDM) and coeliac disease (CD) has been known for a long time 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 and usually extraintestinal symptoms and why only around 10% of them are identified through classic symptoms. 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. Since atypical CD can easily be recognised by determining the antigliadin (AGA), anti-endomysium (AEA) and anti-transglutaminase (tTG) antibodies, the above-mentioned serological tests have been applied to the CD screening of subjects affected by IDDM.

**Epidemiology**

A possible association between IDDM and CD was first reported in 1951 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 (Table 1).

**Table 1. Data on the prevalence of CD in children and adolescents with IDDM.**

<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>
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<td>Ertekin et al. 2006</td>
<td>74</td>
<td>13.5</td>
<td>AGA and EMA</td>
</tr>
<tr>
<td>Hansen et al. 2006</td>
<td>269</td>
<td>12.3</td>
<td>AGA and EMA</td>
</tr>
<tr>
<td>Nimri et al. 2006</td>
<td>42</td>
<td>12</td>
<td>AGA 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 (IgA and IgG)</td>
</tr>
<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>AGA 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. 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.
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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 IgA 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**

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Bone & calcium disorders and coeliac disease

Introduction

Bone and calcium metabolism abnormalities, mainly resulting in osteopoenia and osteoporosis, have long been recognized as a complication of untreated coeliac disease (CD). It has also been reported that, in adults, skeletal disorders may be the only presenting feature of a gluten-sensitive enteropathy (1–3).

The recent availability of simple and reliable biohumoral and instrumental investigations, such as the measurement of bone density by x-ray absorptiometry (DEXA), has allowed to evaluate the frequency and extent of osteopenia and/or osteoporosis in coeliac patients during all stages of the disease, from diagnosis to follow-up (4).

Although bone turnover is also affected by genetic and environmental factors (5), the majority of authors agree that the introduction of a gluten-free diet (GFD) in CD patients results in a significant clinical and metabolic improvement and, in some cases, avoids the progressive deterioration of existing bone alterations (6,7,8). Therefore, it can be easily understood that identification of subjects with untreated CD might play a preventive role, since bone demineralization is associated with a higher risk of fractures.

Definition

Osteoporosis is a systemic skeletal disorder, characterized by bone mass reduction and deterioration of the bone tissue microarchitecture, with a consequent increased susceptibility to fractures (9). From a quantitative point of view, the most widely accepted definition of osteoporosis is based on the evaluation of bone mineral density (BMD), as the World Health Organization (WHO) recently suggested. Osteoporosis is, therefore, defined as a BMD higher than 2.5 standard deviations (SD) below the young adult mean, i.e. when the T-score (the deviation of the individual value from the normal mean value of young adults of the same sex) is lower than 2.5. When the T-score is between 1 and 2.5, an osteopenia condition sets in, a problem requiring an early diagnosis and a suitable treatment, in order to avoid the development of osteoporosis (10).

Epidemiology

A considerable reduction in bone mineral content and density have been reported by several studies in both adults and children with untreated CD, irrespective of the symptomatology at onset (11–15). Although these studies are not homogeneous in terms of selection of patients and controls, and despite some small differences in the adopted research methods, most of them agree that treatment of CD with a strict GFD can improve bone alterations by reducing osteopenia and osteoporosis, halting their progression and decreasing the risk of fractures (13,15).

The extent of bone involvement at the time of CD diagnosis and the metabolic response to the GFD vary considerably among individuals. This mainly depends upon the subject’s clinical and metabolic conditions, age, duration and compliance to GFD. Other additional aspects include genetic and environmental factors (e.g. sex, race, daily calcium intake, level of physical exercise, steroid treatment and, in female subjects, lack of estrogens) (5,6). As all these factors usually overlap, it is quite difficult to estimate the real prevalence of bone disorders in subjects with gluten-sensitive enteropathy.

Therefore, in order to evaluate whether untreated CD is a risk factor for the development of osteopenia and/or osteoporosis, the prevalence of this condition should be estimated in patients in whom no other cause of the above bone disorders has been found. During a U.S. study, 840 subjects were examined - 266 with and 574 without osteoporosis - and subjected to serological screening for CD. The subjects that were positive to either anti-tTG or anti-endomysium antibodies were submitted to intestinal biopsy with the aim of confirming the CD diagnosis. The subjects with CD confirmed by biopsy received gluten-free nutrition and were followed up to evaluate the improvements in bone mineral density. 4.5% of the 266 subjects with osteoporosis and 1% of the 574 subjects without osteoporosis were positive to the serological screening; of these, 9 osteoporotic patients and 1 non-
osteoporotic patient had a positive biopsy. The prevalence of CD confirmed by biopsy was 3.4% among the population with osteoporosis and only 0.2% among subjects without osteoporosis. Anti-tTG levels were correlated with osteoporosis severity, measured by the T-score. Evidence was provided that the more severe the coeliac disease, the more severe the osteoporotic damage. The treatment of coeliac patients with GFD brought about considerable improvements in the T-score. The results of the study have also shown that CD incidence in osteoporosis is sufficiently high to recommend a serological screening for coeliac disease to all patients affected by osteoporosis.

Pathogenesis

Active calcium absorption mainly takes place in the duodenum and the upper jejunum. It is therefore possible to hypothesize that the reduced absorptive surface due to gluten-sensitive enteropathy (villous atrophy, increased intraepithelial lymphocytes and crypt hyperplasia) can also negatively affect the calcium balance. The low serum calcium levels usually found in subjects with untreated CD are, therefore, the main event, subsequently followed by some complex metabolic abnormalities, such as the increased serum parathormone (PTH) concentration.

Not only does PTH hypersecretion promote bone resorption, but it also contributes to determining alterations in vitamin D metabolism. Moreover, the reduced serum calcium levels lead, either directly or through PTH hypersecretion, to an increased activity of 1-a-hydroxylase, the enzyme responsible for the conversion of 1.25-dihydroxycholecalciferol (1.25-OH2-D3) into 25-dihydroxycholecalciferol (25-OH-D2). However, in untreated CD this compensatory effort is totally ineffective because of the target organ inability to respond to the enzyme adequately. This lack of sensitivity is mainly due to a deficiency of proteins involved in the active transport of calcium (e.g., calbindin) and leads to an increase of serum 1.25-OH2-D3 levels. Thus, calcium intestinal malabsorption becomes persistent and so does hypocalcaemia which, in its turn, maintains bone resorption. The rapid disappearance of 25-OH-D3 from coeliac patients' plasma may also suggest an increase in the conversion of this active metabolite into 1.25-OH2-D3, an event mediated by PTH or at least by hypocalcaemia.

In addition to enteropathy, other pathophysiological mechanisms may also contribute to the negative calcium balance usually found in coeliac patients, such as:

1. Low calcium intake with food.
   In CD subjects, the dietary calcium intake is often inadequate, owing to both some degree of anorexia (especially when CD onset occurs in the first years of life), and the typically associated lactose intolerance condition (which can be justified by the mucosal alterations described above). Both factors induce the subject to reduce or even discontinue the intake of milk and its derivatives which, as it is known, are the main calcium source;

2. Low calcium absorption.
   By a feedback mechanism in the parathyroid glands, this event leads to secondary hyperparathyroidism and osteoclast activation, with subsequent calcium resorption from bone tissue in order to maintain the serum calcium levels within normal range;

3. Increased faecal excretion of endogenous calcium
   due to increased intestinal secretion and/or reduced resorption and precipitation of ingested calcium in the intestinal lumen in the form of soaps;

   The results of some studies suggest that GFD supplementation with magnesium results in increased BMD;

5. Low serum levels of Insulin-like Growth Factor 1 (IGF-1).
   IGF-1 is a substance which mediates the anabolic effects of the growth hormone by acting directly on the bone tissue and whose concentrations are directly correlated with the subject's nutritional condition. In both adults and children with active CD, a reduction in the IGF-1 serum levels has been observed. A further hypothesis is that a zinc deficiency, which is frequently observed in coeliac subjects, can play a decisive role in this reduction. Only a total restoration of the intestinal mucosa, after a long treatment based on GFD, can bring the above-mentioned parameters to the normal range.

6. Cytokine production.
   Several studies have demonstrated that, during the active phase of the disease, there is a production of proinflammatory cytokines, such as IL-1, IL-6, TNF-alpha which also seem to carry out a major role in the bone resorption process by stimulating osteoclast differentiation.
Coeliac Disease and activity. Moreover, bone loss can be caused by an imbalance in cytokine production: low blood levels of inhibitory cytokines such as IL-12 and IL-18 are evidence of a failed inhibitory effect on the osteoclastogenesis process (22-25).

Finally, bone resorption can be induced through the activation of the RANKL/OPG cytokine system (26,27). This system, playing a key role in osteoclast biology and bone remodelling, is based on RANKL, a cytokine belonging to the TNF-ligand family, expressed both on the membrane surface of stromal/osteoblastic cells and in soluble form. The system is bound to its RANK receptor, expressed on cells of the osteoclastic line, and stimulates osteoclast differentiation and activation, while inhibiting apoptosis. Osteoprotegerin (OPG) is a further component of this system. It is a soluble cytokine belonging to the TNF-receptor family, expressed by stromal/osteoblastic cells, which acts as a “trap” receptor, with a high affinity for RANKL, to which it binds, thereby preventing RANKL/RANK from binding. An increase in RANKL/OPG has been observed in untreated coeliac subjects.

Clinical and bio-chemical aspects

Bone tissue involvement, commonly found in both children and adults with CD, may occur as one of the presenting clinical and metabolic features but, especially in adults, it can be the only clinical manifestation, even in the absence of any gastrointestinal complaint or before either this or other symptoms become evident. The extent of bone tissue alterations does not appear to be correlated with the presence of pain in the affected skeletal segments or with the severity of intestinal disorders (5). This is the main reason why the bone involvement evaluation requires not only a clinical assessment, but also a series of biochemical investigations (calcemia, phosphoraemia, serum alkaline phosphatase, PTH, vitamin D and bone remodelling markers) and instrumental tests (bone densitometry).

The presence of bone and calcium disturbances in subjects with CD, both at diagnosis and after a variable period of time (8 months – 17 years) from the introduction of GFD, has been evaluated in several studies (5). The majority of these investigations agree in reporting that subjects with untreated CD show the following laboratory and metabolic abnormalities (5,7):

1. a. Hypocalcaemia, increased PTH secretion, decreased serum 25-OHD3 levels with enhanced 1,25-OH2-D3 concentrations and increase of bone remodelling markers. According to some Authors, in adult coeliac patients there is a positive correlation between serum calcium levels and the CD clinical features at onset. Although in all patients with active CD the serum calcium levels are lower than in controls, these values are “better” in subjects affected by subclinical or silent CD than those in subjects presenting with the typical clinical pattern. This relationship has also been observed when the increased bone turnover markers have been taken into consideration. Conversely, the signs and/or symptoms at CD onset do not affect the serum PTH levels (28). Hypovitaminosis D and secondary hyperparathyroidism are common findings in coeliac patients at the onset and in those who do not respond to the dietary treatment, with a reported frequency of 58 - 88 % and 25 %, respectively. In patients responding to GFD, the above-mentioned alterations decrease to 25 and 19 %, respectively (16),

2. BMD reduction. At the onset, coeliac patients show lower BMD values with a reported frequency ranging between 26 and 85%, depending on the examined bone districts and the size of the studied sample (29-31). As regards the existence of a correlation between the clinical expression of CD and the degree of osteopoenia, the data are rather contradictory. From the bio-chemical point of view, it has also been observed that children with untreated CD present with hyperphosphoraemia, mild hypocalcaemia and slightly higher serum PTH levels, with low serum calcitonin levels (32). According to other studies, in paediatric patients, the age at diagnosis plays a more important role than it does in adults, i.e. there is a positive correlation between the age at the time of diagnosis and BMD. Coeliac patients receiving a delayed diagnosis have a lower BMD in comparison with patients who were diagnosed CD at an earlier stage (33).

Finally, the hypothesised role played by hyperparathyroidism secondary to intestinal malabsorption is not sufficient to explain all cases of low bone mass in coeliac patients, who are often affected by
severe skeletal damage, but without evident intestinal symptoms\(^{34,16}\). In this regard, a recent study\(^{23}\) carried out on a group of coeliac patients who had been on a diet for at least two years and on a second group of subjects recently diagnosed and, therefore, not yet on a diet, showed that, despite some patients presenting with a slight increase in PTH levels, secondary hyperparathyroidism does not seem to be the only cause of bone loss in this patients’ sample. The NTx and “Z-score” of bone mass measured in patients do not correlate with the PTH levels, but correlate with a series of osteoclast-stimulating cytokines. Furthermore, the patients’ serum PTH concentration does not correlate with the cytokine levels, thereby suggesting that these are not the consequence of a response to the PTH increase. The high, but still within normal range, levels of excreted calcium, observed in patients not following a diet, induce to think that increased bone resorption can be the main cause of the low bone density. If there were an inadequate calcium resorption due to damaged enterocytes, calcium excretion would be lower in patients not complying to a diet. This generally happens in coeliac patients presenting with evident intestinal symptoms, among which low calcium levels and high PTH levels can often be observed. Altogether, therefore, the authors’ observations support the assumption that cytokine imbalance is an important factor contributing to the bone resorption increase and the subsequent bone mass loss in the studied group of patients. In vitro experiments have shown that the coeliac patients’ sera directly act on both osteoclasts and osteoblasts. In particular, the high NTx levels measured in patients seem to confirm the greater influence of coeliac patients’ serum factors on osteoclasts rather than on osteoblasts. Osteoclastogenesis being stimulated in the presence of suboptimal RANKL concentrations has led to the assumption that this regulator may have been modified in the patients under study. Furthermore, the acceleration in bone loss in coeliac patients appears to be due to a reduction of IL-12 and IL-18 levels. Both cytokines take part in the production of other osteoclastogenesis inhibiting factors\(^{24,28}\); IL-18, for instance, acts on the T-lymphocytes by stimulating them to produce and release GM-CSF\(^{35}\) and both cytokines collaborate to the production of IFN-\(\gamma\)\(^{36,37}\). GM-CSF and the members of the IFN family are known for the inhibiting effect on osteoclastogenesis. It is worth noting that the serum levels of these two cytokines can be different depending on whether coeliac patients are on a diet or not. As a consequence, the contribution made by each cytokine to osteoclastogenesis as a whole will also be different.

**Bone & calcium metabolism and gluten-free diet**

The development of skeletal disorders (especially osteoporosis) is associated with an increased risk of fractures, with evident consequences in terms of population morbidity and mortality. It is, therefore, important to evaluate whether in coeliac patients the presence of a bone demineralization process can be corrected or, at least, stopped in its evolution by starting a GFD. The main purpose of the dietary treatment is to restore a normal intestinal mucosa, so that calcium absorption may take place normally.

**Adult age**

In various studies on the evaluation of bone metabolism in adults, high levels were found for both bone formation and resorption: these results have been ascribed to an increment of bone metabolism following hyperparathyroidism secondary to malabsorption and, as already said, not only that. After the gluten-free diet is introduced, a reduction of both markers can be observed, probably due to the normalisation of PTH secretion\(^{15}\). It is by now known that treatment of CD by complying with a strict gluten-free diet can improve bone alterations by reducing the levels of osteopenia and osteoporosis, halting progression and reducing the risk of fractures\(^{38-13,15}\). However, the data obtained in adults are contradictory: most Authors have reported that in treated coeliac adults the bone mineral content remains below normal average even years after beginning the diet\(^{39}\). Conversely, other studies have found normal values of bone mineral content in adults who had been on a diet for many years\(^{40}\). These discrepancies could also be ascribed to the physiological changes of the bone mass throughout the patient’s life. These depend on the bone mass peak reached in adolescence and the following losses which are the main causes of osteoporosis\(^{41}\).

**Paediatric age**

Studies focusing on the evaluation of bone metabolism alterations in untreated coeliac children have reached different results from studies on adults. In coeliac children, the bone apposition indicators are
low, which is evidence of a limited osteoblast activity associated with an increment in bone resorption activity signalled by high catabolism markers. A diet introduced at paediatric age leads to an increase in bone formation markers as early as a few months later (3 months). These markers even exceed normal values. However, diet introduction does not bring about changes in bone resorption indicators, not even in the long term (15). Thus, the result is higher bone metabolism. The pathogenesis of osteopenia in the untreated paediatric coeliac patients appears to be different from that of adults: studies conducted on children, for example, have not recorded an increment of parathormone, which is indeed present in adults. The existence of a not very well identified element altering the normal regulation of bone modelling has been hypothesized (15). There are data suggesting a possible role for interleukins (IL-1 and IL-6) and anti-bone autoantibodies which in children appear to have a more important role than nutritional alterations in the genesis of CD-correlated osteopenia (42, 43). The studies concerning bone mineral content in children with CD have shown a regression to normal values within one year from the introduction of GFD, with a subsequent increase of height and weight (11, 12, 15). Furthermore, a gluten-free diet has proved to be sufficient by itself, without calcium and vitamin D supplementation per os, to reach a normal mineral content and, as a result, an adequate bone mass peak.

**Conclusions**

The duodeno-jejunal mucosa abnormalities which are typically found in subjects with gluten-sensitive enteropathy make patients at risk of developing skeletal disorders and/or calcium metabolism disturbances which, in some cases, can lead to a progressive deterioration of the bone tissue resulting in osteopenia and/or osteoporosis. The recent availability of laboratory and instrumental tests has allowed to demonstrate that these metabolic problems are common in patients with CD, not only as part of the whole metabolic abnormalities but also, especially in adults, as the only presenting clinical feature of an untreated CD. The introduction of GFD, by allowing a complete recovery of the small intestinal mucosa, leads to the improvement of the bone metabolic and densitometric indexes and, in some cases, even to their full normalization. These findings, together with the existence of an inverse correlation between bone density and risk of fractures, emphasise the preventive role of identifying subjects with untreated CD. Nevertheless, further epidemiological studies involving wider groups of patients with osteopenia and/or osteoporosis are needed, in order to better define whether undiagnosed CD is a significant risk factor for skeletal disease development.
Essential bibliography


Coeliac disease and the liver

Introduction

A wide range of diseases of the liver and biliary system, especially of inflammatory nature, can complicate the clinical course of coeliac disease (CD).\(^{(1)}\)

In general, a distinction can be made between:

- **coeliac hepatitis**\(^{(2)}\); which develops in both patients presenting with intestinal symptoms and subjects with asymptomatic coeliac disease. This benign and clinically silent condition, probably mediated by an immune response, is the most frequent type and can be resolved by a gluten-free diet;
- **autoimmune chronic liver inflammation:** it usually presents itself in the form of autoimmune hepatitis or, sometimes, primary biliary cirrhosis and/or primary sclerosing cholangitis. These, less frequent, disorders require a specific immunosuppressive therapy, as a gluten-free diet (GFD) has not proved to be very effective\(^{(3)}\);
- occasionally, **other types of hepatic lesions** can appear, such as nodular regenerative hyperplasia and hepatocellular carcinoma\(^{(4)}\).

Clinical and epidemiological aspects

The first report of a liver complication in CD dates back to 1977 when hypertransaminasaemia, at CD diagnosis, was found in 30 out of 75 (40%) untreated coeliac patients.\(^{(5)}\) In most cases it can be reversed by introducing a gluten-free diet. Ten years later, an increase in aminotransferase activity was also described in 39 out of 65 (60%) children with gluten intolerance and gastrointestinal symptoms\(^{(6)}\). In the same year, the case of a young girl was reported. She presented with a persistent and cryptogenic elevation of serum aminotransferases and a mild inflammation of the portal tract. In this case, CD diagnosis was suggested by the considerable presence of anti-reticulin antibodies, which was evidence of the fact that this disease can develop atypically as a cryptogenic liver disorder\(^{(7)}\). Two successive retrospective studies confirmed this hypothesis, by showing that more than 9% of patients characterised by a persistent and cryptogenic elevation of serum aminotransferase activity resulted to be affected by asymptomatic coeliac disease.\(^{(8,9)}\) This condition, today known as **coeliac hepatitis**\(^{(2,3)}\), is characterised by:

- Absence of hepatomegaly, splenomegaly or any clinical sign suggesting a chronic liver disease;
- Absence of hypergammaglobulinaemia and serum antibodies (with the exception of CD-specific anti-transglutaminases);
- Presence of a mild inflammation in the globular and portal tracts, which can be reversed by GFD.

An alternative diagnosis is to be taken into consideration, if there is no response after a 12-month GDF treatment\(^{(10)}\). Hyper-transaminasaemia can conceal severe liver damage\(^{(5,11)}\). In these cases, the histological tests may highlight an autoimmune liver disorder characterised by primary biliary cirrhosis (PBC) and/or primary sclerosing cholangitis (PSC) and autoimmune hepatitis\(^{(10)}\). A study\(^{(12)}\) carried out on 4732 adult coeliac patients showed a three times higher risk of developing PBC and PSC in comparison with healthy subjects.

Furthermore, two cases of nodular regenerative hyperplasia (NRH)\(^{(13)}\) have been recently described in patients with gluten-sensitive enteropathy who presented with IgA anticardiolipin antibodies (aCL). The T-help cells deriving from gluten-specific T-cells have been suggested to trigger an IgA response directed against both transglutaminase and the protein/phospholipid complexes, thereby leading to the formation of IgA aCL. The above-mentioned complexes bring about thrombosis in the small radicles of the vena porta, thereby causing hyperplasia in the surrounding tissue\(^{(13)}\).

Table 1 reports the most significant data obtained by a number of studies concerning the association between coeliac disease and liver disorders:
Table 1. CD prevalence in patients with liver disorders.

<table>
<thead>
<tr>
<th>Author</th>
<th>Liver disorder</th>
<th>Nº patients</th>
<th>Nº patients with CD (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bardella et al. (1999)</td>
<td>Hypertransaminasaemia</td>
<td>200</td>
<td>9.3</td>
</tr>
<tr>
<td>Volta et al. (2001)</td>
<td>Hypertransaminasaemia</td>
<td>110</td>
<td>9.1</td>
</tr>
<tr>
<td>Gillette et al. (2000)</td>
<td>Primary biliary cirrhosis</td>
<td>378</td>
<td>2.6</td>
</tr>
<tr>
<td>Volta et al. (2002)</td>
<td>Primary biliary cirrhosis</td>
<td>173</td>
<td>4</td>
</tr>
<tr>
<td>Francavilla et al. (2001)</td>
<td>Autoimmune hepatitis</td>
<td>96</td>
<td>3.4</td>
</tr>
<tr>
<td>Villalta et al. (2005)</td>
<td>Autoimmune hepatitis</td>
<td>47</td>
<td>6.4</td>
</tr>
</tbody>
</table>

Pathogenesis

The pathogenetic mechanism underlying liver damage in coeliac patients is still unclear. The different types of diseases described above may represent a wide spectrum of the same disease in which individual factors, such as genetic predisposition and the duration to gluten exposure, can influence the reversibility of liver damage. Autoimmune liver disorders and coeliac disease do share class-II HLA haplotypes. In the Caucasian population, two haplotypes have been identified as markers predisposing to autoimmune hepatitis: complex HLA A1 B8 DR3 and HLA DR4. Similarly, specific class-II HLA antigens such as HLA-DR3, in particular molecules HLA-DQ2 and HLA DR4, confer genetic predisposition to coeliac disease.

Furthermore, coeliac patients present with increased intestinal permeability which can facilitate the absorption of antigens from the bowel. In genetically predisposed subjects, increased permeability to antigens may induce an immune response against both the antigens sharing common epitopes with the very liver proteins and/or cryptic antigens unmasked by gliadin reaction. Novacek et al. have found a close correlation between the intestinal permeability index and the serum transaminase levels. Finally, it is common knowledge that mucosal damage in coeliac patients leads to the exposure of enzyme tissue transglutaminase, the target antigen recognised by the anti-endomysium antibodies. The hypothesis that this antibody can play a role in extraintestinal CD manifestations, particularly in liver disorders, is corroborated by a recent discovery of extracellular accumulation of IgA-class anti-tissue transglutaminase antibodies in the liver biopsies of two patients with coeliac disease in the active phase.

Conclusions

The close association between coeliac disease and liver disorders calls for an effective screening effort and strict surveillance for CD. The number of coeliac patients who are undiagnosed or untreated is still large and gluten-sensitive enteropathy, complicated by subclinical liver disorders, can in most cases lead to more severe liver damage. As a number of these changes are reversible, much importance has been attached to a timely diagnosis and the adoption of an appropriate gluten-free diet.
Essential bibliography

Coeliac Disease and Malignancy

Introduction

Coeliac disease (CD) is known to be associated with an increased risk of developing malignancy, especially non-Hodgkin lymphoma (NHL) and adenocarcinoma of the small intestine. In 1962, Gough et al. first hypothesised that lymphoma might be a complication of CD.\(^1\) In addition to lymphoma, patients with gluten-sensitive enteropathy show a higher risk of developing various types of epithelial malignancies and, in particular, other tumours such as carcinoma of the larynx and pharynx, cancer of the oesophagus and stomach.\(^2,3\)

Epidemiology

Epidemiological studies suggest a relative risk of developing lymphoma, as a complication of coeliac disease, ranging between 2.1 and 6.6.\(^4^-9\)
Table 1 reports the results of a recent study\(^2\) concerning the evaluation of the CD incidence among two large European populations: one including patients with NHL, the other made up of controls.

Table 1. Odds ratio for NHL in patients with and without coeliac disease\(^2\).

<table>
<thead>
<tr>
<th>Research groups</th>
<th>NHL</th>
<th>Controls</th>
<th>Odds ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Non-CD</td>
<td>CD</td>
<td>Non-CD</td>
</tr>
<tr>
<td>Netherlands</td>
<td>310</td>
<td>7</td>
<td>1009</td>
</tr>
<tr>
<td>Italy</td>
<td>338</td>
<td>1</td>
<td>3262</td>
</tr>
<tr>
<td>UK (Derby)</td>
<td>128</td>
<td>2</td>
<td>451</td>
</tr>
<tr>
<td>UK (London)</td>
<td>25</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Sweden</td>
<td>93</td>
<td>2</td>
<td>1883</td>
</tr>
<tr>
<td>Finland</td>
<td>37</td>
<td>1</td>
<td>59</td>
</tr>
<tr>
<td>Island</td>
<td>87</td>
<td>2</td>
<td>1800</td>
</tr>
<tr>
<td>Ireland (Dublin &amp; Belfast)</td>
<td>38</td>
<td>1</td>
<td>75</td>
</tr>
<tr>
<td>Spain</td>
<td>193</td>
<td>1</td>
<td>241</td>
</tr>
<tr>
<td>France</td>
<td>74</td>
<td>0</td>
<td>491</td>
</tr>
<tr>
<td>Poland</td>
<td>84</td>
<td>0</td>
<td>276</td>
</tr>
<tr>
<td>Serbia</td>
<td>22</td>
<td>0</td>
<td>59</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>1429</strong></td>
<td><strong>17</strong></td>
<td><strong>9606</strong></td>
</tr>
</tbody>
</table>

A study carried out by a team of Italian researchers has analysed the mortality rate among more than 1000 CD patients, diagnosed between 1962 and 1994, and on over 3300 first-degree relatives.

The study showed that the mortality rate (Table 2) significantly exceeds the expected rate (53 deaths as against the 26 expected), especially in the first three years after diagnosis, in patients presenting with malnutrition symptoms and not in those with minor symptoms.

Mortality rate seems to be correlated to a delayed diagnosis and, therefore, to the diet change. Lymphoma is the main cause of death. Conversely, the excess in mortality rate does not concern first-degree relatives.\(^10\)
Table 2. Mortality rate among coeliac patients.

<table>
<thead>
<tr>
<th>Features</th>
<th>Patients</th>
<th>Observed deaths</th>
<th>Expected deaths</th>
<th>SMR (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>258</td>
<td>22</td>
<td>11.0</td>
<td>2.0</td>
</tr>
<tr>
<td>Women</td>
<td>814</td>
<td>31</td>
<td>14.9</td>
<td>2.1</td>
</tr>
<tr>
<td>Age at diagnosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥18-29 years</td>
<td>373</td>
<td>3</td>
<td>1.2</td>
<td>2.5</td>
</tr>
<tr>
<td>30-49 years</td>
<td>507</td>
<td>14</td>
<td>5.9</td>
<td>2.4</td>
</tr>
<tr>
<td>≥50 years</td>
<td>192</td>
<td>36</td>
<td>18.8</td>
<td>1.9</td>
</tr>
<tr>
<td>Compliance to GFD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Good</td>
<td>627</td>
<td>5</td>
<td>10.5</td>
<td>0.5</td>
</tr>
<tr>
<td>Not good</td>
<td>155</td>
<td>26</td>
<td>4.3</td>
<td>6.0</td>
</tr>
<tr>
<td>Uncertain</td>
<td>290</td>
<td>22</td>
<td>11.1</td>
<td>2.0</td>
</tr>
</tbody>
</table>

Clinical patterns

Histologically, the T-cell non-Hodgkin lymphoma, classified by the WHO as ETL (enteropathy-type T-cell lymphoma) (11) is the type of lymphoma most frequently observed in coeliac patients characterised by a clonal proliferation of phenotypically abnormal intra-epithelial lymphocytes (IELs). (12,13) These malignancies can develop in a coeliac patient on a non-strict gluten-free diet (GFD) and insidiously presents itself as a progressive worsening of the patient’s conditions characterised by malaise, anorexia, weight loss, diarrhoea and mild fever, but the onset can be more tumultuous and often complicated by intestinal obstruction with acute abdomen or perforation. Furthermore, a number of studies have also shown an activation of the mucosal associated lymphoid tissue (MALT) in the stomach (follicular gastritis), which may increase the risk of gastric MALT-oma of low malignancy grade. (14) After lymphoma, adenocarcinoma of the small intestine is the neoplasia most frequently associated with gluten enteropathy. (15) Anaemia is the most common presentative finding; other clinical signs and symptoms include weight loss, abdominal pain and intestinal obstruction. (11) Finding a lump at the clinical examination of the abdomen is strongly suggestive of adenocarcinoma, which is much less difficult to diagnose than lymphoma. If the cancer involves the upper gastrointestinal tract, endoscopy usually permits precise definition of the site of the adenocarcinoma. On the contrary, if the tumour is located in the lower gastrointestinal tract, radiological investigation will be able to identify this cancer directly or, at least, through indirect signs (intestinal obstruction). (11,16)

Etiopathogenesis

The reason why some CD patients develop malignancy is still unclear; however, various hypotheses have been made: (17,18)
- impaired function of the immune system and especially of cell-mediated immunity, caused by the villous atrophy and, its consequence, chronic malnutrition;
- chronic inflammation, chronic antigen stimulation and proinflammatory cytokine release;
- absorption of potentially carcinogenic substances, allowed by the increased permeability of the intestinal mucosa;
- presence of lesions with pre-malignant features in the intestinal mucosa of untreated CD patients, such as an increased mitotic activity in the crypts and irregularities in the surface of the epithelium.

Risk of malignancies and dermatitis herpetiformis (DH)

<table>
<thead>
<tr>
<th>Author</th>
<th>Patients with DH (n)</th>
<th>Malignancies (n)</th>
<th>RR (Relative Risk)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sigurgeirsson B et al. 1994</td>
<td>976</td>
<td>94</td>
<td>1.4 M – 1.2 F</td>
</tr>
<tr>
<td>Collin P et al. 1996</td>
<td>305</td>
<td>13</td>
<td>1.25</td>
</tr>
<tr>
<td>Askling J et al. 2002</td>
<td>1128</td>
<td>135</td>
<td>1.2</td>
</tr>
</tbody>
</table>
Gluten-free diet (GFD) and risk of malignancy

Withdrawing gluten from the diet of CD patients leads to a progressive and full recovery of the small intestinal mucosa. Moreover, in almost all cases, if gluten is reintroduced, a mild to severe villous atrophy appears again where the above-described epithelial alterations produced lesions which could lead to the onset of cancer. It is therefore reasonable to think that maintaining a normal intestinal mucosa by sticking rigorously to GFD can be a preventive factor against tumour onset. Some studies\(^\text{10,21}\) have demonstrated that CD patients who had rigorously followed the GDF for 5 or more consecutive years, showed the same risk of malignancy as the general population. This risk was found to be significantly higher in coeliac patients on a normal or a low gluten containing diet.

Conclusions

The relationship between CD and malignancy, irrespective of type (lymphomas or others) and site (intestinal or extraintestinal), is by now a fact. However, there is as yet no specific serological and/or histological marker available which would allow early identification of those CD patients at risk of developing cancer. Furthermore, the extent to which the coeliac risk factor affects the development of malignancy is still unknown. However, data resulting from published studies seem to corroborate the hypothesis that untreated CD exposes the patient to a greater risk of developing malignancy. At present, therefore, most Authors agree that all coeliac patients should be advised to follow a strict gluten-free diet which, in these cases, actually plays a mainly preventive role.

Bibliography

Neuro-Psychiatric Disorders and Coeliac Disease

Introduction

The association between coeliac disease (CD) and neuro-psychiatric disorders has long been known and has been described in both adults and children.\(^1\) \(^6\) Neurological problems can be found in association with typical signs and symptoms of CD, but they are often the only presenting symptom of gluten-sensitive enteropathy.\(^4\) \(^7\) \(^8\)

Epidemiology

The prevalence of the association between CD and neuro-behavioural disturbances is difficult to evaluate and is rather variable.

Most reports concern the association between CD and cerebellar ataxia\(^4\) \(^2\) \(^9\) \(^10\), sensory-motor and autonomic neuropathy\(^11\), epilepsy\(^12\) \(^\text{-}17\), dementia, headache, anxiety, irritability and depression\(^11\) \(^18\) \(^\text{-}21\). In the past, Cooke and Smith\(^2\) were the first to describe a group of 16 coeliac patients with gait ataxia and peripheral neuropathy. Later, a team of British neurologists who, as early as 1996\(^1\), highlighted the strong prevalence (57%) of undetected CD in subjects with neurological diseases, mostly ataxic patterns, defined this condition as gait ataxia\(^23\). This is often associated with peripheral neuropathy with signs of cerebellar atrophy. In subjects affected by this disease, signs of an immune response to gluten (AGA) are increasingly observed\(^10\) \(^11\) \(^24\) \(^\text{-}26\), with autoantibodies directed against Purkinje cells\(^6\), displaying positivity for CD-specific antigens of the HLA system\(^27\). However, only half of the cases present with the typical histological lesions in the intestinal mucosa.

The duration of gluten exposure seems to be directly correlated to ataxia severity and indirectly correlated to the efficacy of a gluten-free diet as a treatment for symptom regression\(^7\) \(^28\) \(^\text{-}30\). The first evident association between coeliac disease, occipital endocranial calcifications and epilepsy, later confirmed by numerous additional studies\(^12\) \(^\text{-}17\), dates back to 1970\(^3\). These are serpiginous calcifications of vascular origin. Before the syndrome was definitely recognised, some cases were classified as atypical Sturge-Weber syndrome given the similarity of the cerebral calcifications to the findings in real Sturge-Weber cases at the computed tomography (CT) examination, but without facial angioma or mental retardation.

Clinically, patients present with patterns of partial occipital drug-resistant epilepsy, without clear signs of malabsorption. With regard to this relation, the autoimmune hypothesis has also been suggested. There is strong evidence showing that a gluten-free diet (GFD) can lead to a better control of seizures and a reduction in the use of antiepileptic drugs, but does not achieve a full resolution of seizures\(^3\).\(^2\)

A recent Israeli study\(^3\) has found that one or more common neurological disorders (such as hypotonia, retarded development, learning disorders, attention deficit/hyperactivity disorder, headache and cerebellar ataxia itself) are present in 51.4% of coeliac children, a significantly greater prevalence than that found in the control population (19.9%). The study clearly demonstrates the effectiveness of a GDF at least on hypotonia in babies and on headache. Finally, other clinical trials showed that autistic children present with histological intestinal alterations that are similar to those of CD patients, even though a direct association between autism and coeliac disease has never been proven. However, data concerning the effectiveness of a gluten-free diet in autistic children are contradictory\(^6\).

Tables 1 and 2 report the main findings on the frequency of these disorders, in adult and paediatric patients respectively.

### Table 1. Prevalence of neuro-behavioural disorders in adult CD patients and vice-versa.

<table>
<thead>
<tr>
<th>Author</th>
<th>CD patients</th>
<th>Neurological Disorders (%)</th>
<th>Behavioural disorders (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Luostarinen L et al. (1999)(^4)</td>
<td>144</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Roche-Herrero MC et al. (2001)(^14)</td>
<td>86</td>
<td>39.5</td>
<td>10</td>
</tr>
<tr>
<td>Cicarelli G et al. (2003)(^11)</td>
<td>176</td>
<td>49</td>
<td></td>
</tr>
<tr>
<td>Zeinik N et al. (2004)(^9)</td>
<td>111</td>
<td>51.4</td>
<td></td>
</tr>
</tbody>
</table>
Table 2. Prevalence of CD in patients with neuro-behavioural disorders.

<table>
<thead>
<tr>
<th>Author</th>
<th>Patients with neuro-behavioural disorders (n°)</th>
<th>Coeliac Disease (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pellecchia MT et al. (1999)</td>
<td>24</td>
<td>12.5</td>
</tr>
<tr>
<td>Burk K et al., (2001)</td>
<td>104</td>
<td>1.9</td>
</tr>
<tr>
<td>Bushara KO et al. (2001)</td>
<td>50</td>
<td>37 e 27</td>
</tr>
<tr>
<td>Gabrielli M et al. (2003)</td>
<td>90</td>
<td>4.4</td>
</tr>
<tr>
<td>Chin RL et al. (2003)</td>
<td>20</td>
<td>8</td>
</tr>
</tbody>
</table>

Clinical aspects

The neuro-behavioural disturbances described in CD patients include rather heterogeneous clinical patterns, which vary with the type of disease and the patient’s age. Tables 3 and 4 report the neurological disorders and behavioural changes most frequently observed in adults and children affected by CD.

Table 3. Neurological disorders in CD patients.

<table>
<thead>
<tr>
<th>Adulthood</th>
<th>Childhood</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ataxia 4(9,10)</td>
<td>Epilepsy 14,37</td>
</tr>
<tr>
<td>Peripheral neuropathy 11</td>
<td>Autism 6</td>
</tr>
<tr>
<td>Epilepsy 15-17</td>
<td>Migraine 33</td>
</tr>
<tr>
<td>Pre-senile dementia 6</td>
<td>Migraine 35</td>
</tr>
<tr>
<td>Cerebellar disorders 37</td>
<td></td>
</tr>
</tbody>
</table>

Table 4. Personality and behavioural changes in CD patients 11, 20, 21, 33

<table>
<thead>
<tr>
<th>Adulthood</th>
<th>Children</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depression</td>
<td>Irritability</td>
</tr>
<tr>
<td>Anxiety</td>
<td>Apathy</td>
</tr>
<tr>
<td>Schizophrenia</td>
<td></td>
</tr>
</tbody>
</table>

Of the possible psychiatric complications, depression is the most frequent, especially in adults. Few studies have addressed this issue in childhood, as a standardised evaluation of children’s cognitive-behavioural abilities is quite complex to perform. However, the most important reported data mainly concern mood disturbances, such as irritability and apathy.

Pathogenesis

The nature of the association between CD and neurological disorders has not been clearly defined yet and several mechanisms may be involved:

Disorders of the peripheral nervous system

- Folic acid, vitamin B12, and pyridoxine deficiencies caused by intestinal malabsorption.
Degenerative disorders of the central nervous system

- Vitamin E deficiency due to lipid malabsorption\(^{(39)}\).
  However, the results of studies addressing this issue are rather contradictory, since the symptoms related to the involvement of the cerebellar area can also be found in subjects with normal serum levels of vitamin E. Over the past ten years, an increasing number of authors have suggested that, in most patients, an ongoing immune-mediated inflammatory process, lymphocyte infiltration or vasculitis of the central nervous system can cause irreversible neuronal, glial or axonal damage\(^{(8)}\).

Epilepsy and cerebral calcifications

- Folic acid deficiency due to intestinal malabsorption,\(^{(40)}\) with subsequent alteration of lecithin metabolism (lecithins are the main constituent of myelin), and microangiopathic myelinisation of the cerebral cortex vessels and the basal nuclei, with calcific deposits in the altered organic matrix. This hypothesis is extremely interesting and would explain the cause-effect relationship between malabsorption and the origin of cerebral calcifications. However, epilepsy and cerebral calcifications can also be observed in subjects without CD and with normal folic acid serum levels.\(^{(41)}\)
- Immunological hypothesis.\(^{(42)}\) As CD can be associated with various autoimmune disorders, it is impossible to exclude the possibility that cerebral calcifications depend on an autoimmune or inflammatory process related to the presence of immune complexes. Immune pathogenetic mechanisms have also been considered when interpreting more complex neurological disorders, such as dementia and cerebral atrophy.
- The association between CD, epilepsy and cerebral calcifications could be part of a genetically determined syndrome.\(^{(27)}\)

Behavioural disturbances

- Abnormal amino acid levels.
  Recent studies have found that both untreated and treated coeliac children show lower plasma tyrosine and tryptophan concentrations than controls.\(^{(6)}\)

Conclusions

The association between neuro-psychiatric disorders and CD is likely to be more common than previously thought. Moreover, these disturbances are often the only presenting complaint of an untreated gluten-sensitive enteropathy. All patients, whose symptoms are suggestive of a central and/or peripheral nervous system disorder, as well as those with behavioural disturbances should be thoroughly checked for possible CD. Furthermore, special care should be given to those patients affected by seizures (epilepsy) with poor response to drugs. Although coeliac patients with neuro-behavioural disorders often present with a low-grade intensity illness, they should always be advised to follow a gluten-free diet (GFD). In most subjects affected by epilepsy, GFD can have positive effects on the evolution of the neurological disorder, as the recovery of the small intestinal mucosa is followed by an improved response to the drug therapy and, therefore, by a reduction in the frequency and intensity of seizures.
Coeliac Disease and.....

Bibliography

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Pediatrics 2004;113:1672-76.
Fertility and coeliac disease

Introduction

Coeliac disease (CD) is an important reproductive risk factor for both genders, as it can exacerbate problems related to nutritional deficiencies that, through various mechanisms, can interfere with the endocrine and immune systems of both men and women (1).

Clinical and epidemiological aspects

By examining the clinical and epidemiologic studies available in the literature, a coherent set of reproductive tract disorders related to CD can be outlined. The reproductive alterations most frequently found in women affected by CD include: infertility (2,3), spontaneous abortions (4), amenorrhea and shorter fertility period (delayed puberty, early menopause) (5-8). Moreover, delays in the intrauterine foetal growth are not excluded (10).

Infertility

In a case-control study on women with infertility for unexplained reasons (2), 4.1% (4 out of 98 patients) of the cases were affected by CD in comparison to 0 out of 150 controls. Even more recent studies have confirmed a higher CD incidence in women with infertility problems (3). Thus, it seems possible that, in some patients, unexplained infertility can be the consequence of a clinically silent disease, it being its first and, sometimes, only symptom. However, the correlation between infertility and coeliac disease remains controversial. The results of a recent study (9) show that fertility of CD women is similar to that of general female population, but at an older age. Data of 521 coeliac women were compared with those of 7732 non-coeliac women. The percentage was 48.2 and 47.7 live births per 1000 people-year for coeliac and non-coeliac women respectively. The fertility percentage, specific by age, showed that coeliac women have a lower fertility if younger, but a greater fertility if older than non-coeliac women. This increment in relative fertility remained with age, regardless whether women had been subjected to CD treatment or not. Finally, the lower fertility of coeliac women may be correlated not as much to the difficulties in conceiving as to problems arising during pregnancy, such as recurrent abortions and intrauterine death.

Spontaneous abortion

A study on untreated coeliac patients (4) reported a 17.8 % prevalence of abortion. This percentage can go down to 2.4 % if an adequate diet is introduced. This difference is even more evident if only patients with repeated abortions are considered, for whom a gluten-free diet (GFD) can reduce the risk nine-fold (43.3 % vs. 7.7 %). Therefore, women with a history of multiple abortions should be submitted to clinical tests for CD (10).

Menarche and alteration of the menstrual cycle

Coeliac women, even if affected by subclinical CD, have their menarche at an older age. A case-control study carried out on 180 women in Italy in 1990 (5) reported that the menarche takes place at about 13.5 years of age among the coeliac population, whereas in normal subjects this event occurs at 12 years of age. In more recent times, another study (6), on analysing the menstrual history of 200 Brazilian women, proved a significant delay in puberty in coeliac patients in comparison to the control group, including patients with irritable colon syndrome (IBS). This difference, although more evident in subjects with a severe nutritional state, was also observed in subjects presenting with an adequate nutritional state, but who continued to assume gluten. In coeliac patients not complying with the gluten-free diet, a greater frequency of secondary amenorrhea has also been found. In one study (6), secondary amenorrhea was present in 38.8 % of women with untreated CD, in comparison to 9.2 % of non-coeliac women used as controls; in another study (8) this was observed in 28% of coeliac women, with a different prevalence depending on whether they complied with a gluten-free diet or not (respectively 12.5 % and 30.0 %) and irrespective of their nutritional state. These data are particularly important in relation to a study (7) mentioning previous amenorrhea among the risk factors of postmenopausal osteoporosis in women.
**Age at menopause**

An example is given by a research study\(^6\) according to which the mean age of CD women with was younger (approx. 47.6 years) as against the non coeliac women used as controls (approx. 50.1 years). These data call for a reflection, in the sense that, as the age at menopause gets younger among CD women, the risk of developing osteoporosis at an earlier age increases; like in the case of amenorrhea, age at menopause is included among risk factors for osteoporosis.\(^7\)

**Unfavourable pregnancy outcomes**

Epidemiological studies have shown that children born from coeliac women have a greater risk of low weight birth and greater risk of delayed foetal growth. Furthermore, recent studies have found that these female reproductive disorders are more frequent among undiagnosed coeliac women \(^{11,12}\) (table 1) and that the restoration of the intestinal mucosa leads to an improvement of the foetal nutritional support which also affects the overall perinatal outcome.\(^{13}\)

**Table 1. Unfavourable pregnancy outcomes.**

<table>
<thead>
<tr>
<th></th>
<th>Percentage with unfavourable pregnancy outcomes (N %)</th>
<th>Odds ratio 95% CI OR</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>IUGRa</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No CD</td>
<td>88,073/2,806,297 (3.1)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Undiagnosed CD</td>
<td>51/923 (5.5)</td>
<td>1.80; 1.36–2.39</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Diagnosed CD</td>
<td>39/1,141 (3.4)</td>
<td>1.09; 0.79–1.50</td>
<td>.588</td>
</tr>
<tr>
<td><strong>Low birth weight</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No CD</td>
<td>95,531/2,814,664 (3.4)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Undiagnosed CD</td>
<td>65/926 (7.0)</td>
<td>2.15; 1.67–2.76</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Diagnosed CD</td>
<td>47/1147 (4.1)</td>
<td>1.22; 0.91–1.63</td>
<td>.137</td>
</tr>
<tr>
<td><strong>Extremely low birth weight</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No CD</td>
<td>14,567/2,814,664 (0.5)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Undiagnosed CD</td>
<td>11/926 (1.2)</td>
<td>2.31; 1.28–4.19</td>
<td>.006</td>
</tr>
<tr>
<td>Diagnosed CD</td>
<td>6/1147 (0.5)</td>
<td>1.01; 0.45–2.25</td>
<td>.979</td>
</tr>
<tr>
<td><strong>Preterm birth</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No CD</td>
<td>139,921/2,815,329 (5.0)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Undiagnosed CD</td>
<td>74/925 (8.0)</td>
<td>1.66; 1.31–2.11</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Diagnosed CD</td>
<td>72/1,146 (6.3)</td>
<td>1.28; 1.01–1.63</td>
<td>.041</td>
</tr>
<tr>
<td><strong>Extremely preterm birth</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No CD</td>
<td>9,548/2,815,329 (0.3)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Undiagnosed CD</td>
<td>6/925 (0.6)</td>
<td>1.92; 0.86–4.28</td>
<td>.112</td>
</tr>
<tr>
<td>Diagnosed CD</td>
<td>4/1146 (0.3)</td>
<td>1.03; 0.39–2.75</td>
<td>.954</td>
</tr>
</tbody>
</table>
Coeliac Disease and male reproductive system

With regard to the effects of coeliac disease on the male reproductive system, men, too, run a risk of higher infertility and other reproductive disorders in addition to a greater incidence of hypoandrogenism. Interestingly, the presence of CD in the father is also a risk factor of low birth weight for his offspring. A study by Ludvigsson 10,597 low birth weight babies, observed t
a reportables had coeliac mothers, 27 babies had coeliac fathers, 70 babies had coeliac siblings and 442 had both parents affected by CD. Babies with coeliac fathers weighed less than babies with non-coeliac fathers and, also, less than babies with fathers affected by other autoimmune diseases. In particular, newborns with coeliac mothers weighed 222 g less than the average population and newborns with coeliac fathers weighed 266 g less; for coeliac fathers, the risk of having low birth weight babies was 5 times higher than that of the general population (11 vs 2.5%).

Pathogenesis

At present, the pathogenetic mechanism underlying the genito-reproductive system disorders is unknown; however, the following hypotheses have been suggested:

- Alteration of the nutritional state and micronutrient deficiency (iron, zinc, folic acid, vitamin B12, vitamin B6, vitamin K). With regard to the chronic malabsorption of vitamins, in CD folic efficiency is very well known (15,16). Folin CD ic acid is an essential vitamin for the metabolism of nucleic acids, a deficit which particularly affects the tissues characterised by rapid proliferation, such as the haemopoietic system, the embryo and the seminiferous epithelium. Furthermore, in male subjects, deficiencies of liposoluble vitamins, such as vitamin A(17) and E(18,19) are not to be underestimated. Vitamin A, regarded as a protection factor for the epithelia, plays a major role in the functionality of Sertoli cells as well as in the first stages of spermatogenesis(20). Vitamin E, an antioxidant factor, plays various important roles in male reproductive health, such as the correct differentiation and functionality of the epididymal epithelium, the maturation of spermatic cells(21) and the secretion of proteins by the prostate(22). Moreover, the antioxidant effect can be protective for agents carrying out an endocrine activity(23), many of which have testicular stroma and seminiferous epithelium as specific targets.

- 5 alpha-reductase deficit. Tissue reencystance of the hormones circulating in men with gluten enteropathy and intestinal villous atrophy has been suggested as a cause. In particular, gonadic dysfunction is thought to be due to the reduction of testosterone conversion into DHT caused bdihydrotestosterone (y t)he low levels of 5 alpha-reductase (an enzyme responsible for the reduction of testosterone into alpha-dihydrotestosterone in males). In CD, this leads to the disruption of the hypothalamic-pituitary axis(1).

- Immune mechanisms: it should be clarified that the HLA locus involved in the predisposition to CD is also important for other autoimmune diseases. DPG could onGFD estore the normal micronutrient absorption, but not other mechanisms that may have been triggered off. Furthermore, overt CD can reactivate or appear during the last stage of pregnancy or during breast-feeding. This may suggest that, also under these circumstances, immune and hormonal alterations that are typical of pregnancy or puerperium can play a role(24);

- Oxidative stress can be associated with chronic CD, with a subsequent increase in free radicals of lipid and protein origin. The activity of the xanthine oxidoreductase system in the bowel is one of the main sources of free radicals and is much more evident in CD of the clclassic asr, even subclinical CD can be characterised by an oxidoreductive imbalance shown by plasma indicators, such as carbonilic groups of protein origin.(26)
Coeliac Disease and.....

Conclusions

In the past years, reports on the existence of a possible association between coeliac disease and reproductive tract disorders have increased. As reproductive alterations are reversible, a timely diagnosis and the introduction of a gluten-free diet are of paramount importance. Thus, the use of early CD indicators, such as vitamin and/or iron deficiencies, andrologic or endocrinologic dysfunctions, should allow a prompt adoption of prevention and treatment strategies.

Essential bibliography