Coeliac disease and autoimmune thyroid disease

C E Counsell, A Taha, W S J Ruddell

Abstract
A well defined cohort of coeliac patients was studied prospectively to assess the prevalence of coexisting thyroid disease and positive thyroid autoantibodies. Comparison with epidemiological data on the prevalence of coeliac disease in a neighbouring area suggested that few adult coeliac patients had been missed. Overall, 14% of the coeliac patients had thyroid disease: 10-3% were hypothyroid and 3-7% hyperthyroid, both significantly more than expected. There were significantly more coeliac disease patients with thyroid autoantibodies than expected —11% had thyroglobulin antibodies and 15% had thyroid microsomal antibodies. This association is clinically important. Three patients are described in whom the coexistence of coeliac disease and hypothyroidism led to diagnostic difficulties and delay of treatment.

Case reports

CASE 1
A 27 year old woman presented with constipation and menorrhagia. Investigation showed a normal haemoglobin (12 g/dl); mild iron deficiency, with a serum iron of 10 μmol/l (normal range 11–30 μmol/l); and autoimmune hypothyroidism: thyroid stimulating hormone (TSH) 109 mU/l (normal range 0.4–5.0 mU/l), thyroxine T₄ 19 nmol/l (normal range 70–155 nmol/l), thyroglobulin antibodies titre 1/640. She was started on thyroxine but despite adequate replacement therapy (TSH 1-2 mU/l) she lost 28 lb in weight and developed diarrhoea. Further investigation showed continued iron deficiency and new folate deficiency. Distal duodenal biopsy specimens showed subtotal villous atrophy and there was a noticeable clinical response to a gluten free diet. Repeat biopsies six months later confirmed significant histological improvement.

CASE 2
An 80 year old lady had been on replacement thyroxine for 20 years and was biochemically euthyroid (TSH 2.0 mU/l, thyroxine T₄ 90 nmol/l). She gave a long history of diarrhoea resistant to all previous therapy and thought to be due to thyroxine treatment. She was found to have mild iron and folate deficiency (serum iron 9 μmol/l, serum folate 2.0 μg/l). Distal duodenal biopsy specimens showed partial villous atrophy and there was an excellent clinical and histological response to a gluten free diet.

CASE 3
A 26 year old woman presented with lethargy, a macrocytic anaemia of 9 g/dl (mean cell volume 98 fl), but no gastrointestinal upset. She was found to have a low serum iron but normal vitamin B12 and folate values. Distal duodenal biopsy specimens confirmed subtotal villous atrophy. There was some initial response to a gluten free diet with an increase in her weight and haemoglobin (11 g/dl). Her lethargy and macrocytosis persisted, however, and she developed menorrhagia. She was subsequently found to be severely hypothyroid (TSH 185 mU/l, free thyroxine T₄ <4 pmol/l, thyroid microsomal antibodies 1/800). Thyroxine supplementation led to resolution of her symptoms, and a return to normal of her haemoglobin (13 g/dl), mean cell volume (89 fl) and TSH (4.5 mU/l). Repeat duodenal biopsies after six months of her diet showed significant improvement.
Coeliac disease and autoimmune thyroid disease

TABLE I: Observed and expected number of cases of thyroid disorders in 107 adults with coeliac disease

<table>
<thead>
<tr>
<th>Hypothyroidism</th>
<th>Hyperthyroidism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observed No</td>
<td>Expected No</td>
</tr>
<tr>
<td>Men</td>
<td>2</td>
</tr>
<tr>
<td>Women</td>
<td>0</td>
</tr>
<tr>
<td>Total (%)</td>
<td>11 (10-3)</td>
</tr>
</tbody>
</table>

TABLE II: Observed and expected number of adult coeliac patients with thyroid autoantibodies

<table>
<thead>
<tr>
<th>TG antibodies</th>
<th>TM antibodies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observed No</td>
<td>Expected No</td>
</tr>
<tr>
<td>Men</td>
<td>3</td>
</tr>
<tr>
<td>Women</td>
<td>9</td>
</tr>
<tr>
<td>Total (%)</td>
<td>12 (11-2)</td>
</tr>
</tbody>
</table>

TABLE III: Standardised ratios and 95% confidence intervals (95% CI)

<table>
<thead>
<tr>
<th>Hypothyroidism</th>
<th>Hyperthyroidism</th>
<th>TG antibodies</th>
<th>TM antibodies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observed No</td>
<td>Expected No</td>
<td>Standardised ratio (95% CI)</td>
<td>Observed No</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>11</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>4</td>
<td>0</td>
<td>7</td>
</tr>
<tr>
<td>TG antibodies</td>
<td>12</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>TM antibodies</td>
<td>16</td>
<td>8</td>
<td>3</td>
</tr>
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</table>

Patients and methods
A review of the medical and dietetic registers and patients attending the gastroenterology clinic identified 107 adult patients with coeliac disease attending Falkirk Royal Infirmary. The hospital serves a population of 147 000 people. The mean age was 46 years (range 16 to 82 years), and there were 72 women and 35 men.

Coeliac disease was diagnosed on the basis of the clinical history, consistent histological changes seen on distal duodenal or jejunal biopsy specimen and a good clinical response to a gluten free diet. In addition, 75 patients (70%) had a repeat biopsy after six months' treatment which showed a significant histological improvement.

All the patients were reviewed in the gastroenterology clinic and had thyroid function and thyroid antibodies measured. Standard radioimmunoassays for total and free T₃ and T₄ and for TSH were used. Thyroid microsomals (TM) and thyroglobulin (TG) antibodies were measured using agglutination techniques.

Hypothyroidism was diagnosed on the basis of a raised TSH and a low thyroid T₃ or T₄ value, or both. Similarly hyperthyroidism required a suppressed TSH with a raised thyroxine T₃ or T₄ value, or both. In addition, the clinical histories and the case notes were reviewed for evidence of previously documented thyroid disease. The figures presented for the prevalence of thyroid disease include such previously diagnosed patients (mainly hypothyroid patients now on thyroxine with normal thyroid function) together with newly diagnosed cases. None of the patients in this study had iatrogenic thyroid disease.

We compared our findings with the expected prevalence of spontaneous overt hypothyroidism and hyperthyroidism and of thyroid antibodies in patients without coeliac disease. This was based on the figures published by Tunbridge et al for an adult community in north east England. They found that 1-9% of women and 0-16% of men were overtly hypothyroid, 1% of women and less than 0-1% of men were hyperthyroid, 10-3% of women and 2-7% of men had TM antibodies, and 3-0% of women and 0-9% of men had TG antibodies.

The results were analysed by calculating the standardised ratios (observed number/expected number) for each category. The 95% confidence intervals were calculated using the exact Poisson calculation for standardised ratios from the BMJ Confidence Interval Analysis program. Where the confidence interval does not contain 1-00 the ratio can be regarded as significant.

Results
The results are shown in Tables I, II, and III. They were complete except for one female patient in whom the thyroid antibodies were unknown. They show a significantly greater proportion of coeliac patients with hypothyroidism (10-3%), hyperthyroidism (3-7%) and with both TG (11-2%) and TM (15%) autoantibodies than expected. The overall prevalence of 14% for overt thyroid disorder in patients with coeliac disease is of considerable clinical importance. The mean age of those with both coeliac and thyroid disease was significantly higher than that of those with just coeliac disease (53-8 years compared with 44-1 years: Student’s t test, p<0-0001).

In 11 of the 15 patients with both diseases (eight with autoimmune hypothyroidism, three with hyperthyroid Graves’s disease), the thyroid disease had presented first. All had received adequate treatment and were euthyroid at the time their coeliac disease was diagnosed. Three (two hyperthyroid, one hyperthyroid) were found to have overt thyroid disease at the time their coeliac disease was diagnosed. All three had IgA anti-gliadenn antibodies. They were each started on a gluten free diet at about the same time they received appropriate treatment for their thyroid disease. In one patient (case 3) hypothyroidism was diagnosed five months after the coeliac disease and thyroxine supplements were started before a repeat duodenal biopsy was performed.

Discussion
Retrospective studies based on case notes review have suggested that between 2.7% and 5.8% of coeliac disease patients are hypothyroid. We believe that we have quantified this association more accurately by prospectively measuring thyroid function and autoantibodies in addition to seeking a previous history of thyroid disease in all coeliac patients identified within a defined population in central Scotland.

Studies of the prevalence of coeliac disease have shown significant regional variation. In West Lothian, a neighbouring area of Scotland served by a gastrointestinal unit with a strong...
interest in coeliac disease, the prevalence of coeliac disease in adults is 45 per 100 000.3 This suggests that our own prevalence of 73 per 100 000 is reasonably accurate and that this study is therefore based on as complete a population of coeliac disease patients as possible. Untreated hypothyroidism and hyperthyroidism can both give rise to histological changes in the small bowel similar to those of coeliac disease,4,7 making diagnosis difficult. These changes revert to normal, however, with adequate treatment of the thyroid disorder.4,7 Given that all except four of our patients were known to be euthyroid at the time their coeliac disease was diagnosed, we do not feel this biased our results. We also felt it reasonable to include the three patients in whom the thyroid and coeliac disease were diagnosed concurrently as all had IgA anti-gliadin antibodies.

Unfortunately, no separate data exist on the prevalence of thyroid disease in the Forth Valley and therefore this information was calculated using data from the Whickham study in north east England.8 We felt this was reasonable, however, as two hospital based studies in Scotland have shown point prevalences of hyperthyroidism and hypothyroidism similar to those found in Whickham.9,10

We have therefore shown that the risk of overt thyroid disease, particularly hypothyroidism, in coeliac patients is greater than was previously believed. In addition, there was a greater than expected prevalence of thyroid antibodies, and a proportion of these patients will go on to develop overt hypothyroidism.11 This association between coeliac disease and autoimmune thyroid disease is not surprising given that the HLA haplotypes B8 and DR3 are found more commonly in both than in the general population.12-14

The patients with both coeliac and thyroid disease were significantly older than those with coeliac disease alone. This may be simply because the prevalence of hypothyroidism increases with age.8 Another reason may be that the longer patients with coeliac disease remain untreated the more likely they are to develop autoimmune thyroid disease. Perhaps the abnormal small bowel mucosa allows excessive amounts of certain antigens to enter the circulation which cross react with thyroid antigens. Hence early detection of coeliac disease and commencement of a gluten free diet may reduce the risk of developing thyroid disorders. In our series only one of the 15 patients with coeliac and thyroid disease had been on a gluten free diet before the diagnosis of the thyroid disease, and then only for five months. This could be investigated further by assessing the prevalence of thyroid disorders in long term follow up of children with coeliac disease who were started on a gluten free diet early.

The association of coeliac disease and hypothyroidism is important clinically. Both diseases can present with lethargy, macrocytic anaemia, bowel disturbance, and malabsorption. Failure to recognise and treat both can therefore result in an apparent lack of response to treatment, as in the third patient presented here. There may, however, be clues to their coexistence such as the persistent macrocytosis in the face of normal haematins, as in our patient 3. Untreated hypothyroidism can also mask the weight loss and diarrhoea of coeliac disease, as in the first case presented. These symptoms appeared only after thyroxine supplementation.

On the basis of our findings we suggest that thyroid function should be checked routinely in all coeliac patients at presentation, and rechecked if symptoms or a macrocytosis fail to respond to a gluten free diet. Similarly coeliac disease should be considered in hypothyroid patients who fail to respond to thyroxine or develop weight loss or diarrhoea.

We would like to thank Dr David Gordon of the Department of Public Health Medicine at the Forth Valley Health Board for his help with the statistics.

6 Kelly ML, Stewart JM, Nyssedem and intestinal malabsorption (nontropical Sprue?) with severe hypomobility of the gastrointestinal tract. Am J Dis Dig 1964; 7: 79-86.