Coeliac disease screening in children with type 1 diabetes mellitus: is it time for a new approach?

Eleanor Duckworth1
BA, MB BChir, F2 Doctor

Sejal Patel2
BSc, MBChB, Specialty Registrar

Taffy Makaya2
MBChB, MMedSci, Consultant Paediatrician

1Oxford Foundation School, Oxford Deanery, UK
2Department of Paediatric Diabetes, Oxford Children’s Hospital, Headington, UK

Abstract
NICE guidelines recommend annual screening for autoimmune thyroid disease (ATD) in children with type 1 diabetes mellitus (TIDM), but only one initial screen for coeliac disease (CD) at TIDM diagnosis and thereafter if symptomatic. Our study aimed to assess the relationship between the diagnosis of CD and TIDM within our local population, and review the current screening guidelines.

We performed a cross-sectional review of patients attending the Oxfordshire Paediatric Diabetes Service to identify those with CD and ATD. Further analysis established how the diagnosis of CD had been made, and the timing of the diagnosis.

Of the 342 children within the Oxfordshire Paediatric Diabetes Service, we identified 28 patients with CD (8.2%) and 20 with ATD (5.8%). Only 28% of CD diagnoses were made from initial new diabetic screening bloods, whereas 56% were diagnosed from annual review bloods. One patient (4%) presented with symptoms outside annual review. Forty-four percent of the cohort were diagnosed with CD within the first year of TIDM diagnosis but 12% were diagnosed after five years with TIDM.

Our results show a higher prevalence of CD than previous literature has suggested. The majority of cases were asymptomatic and identified by annual review bloods after initially negative screening tests. We recommend that national guidelines should be re-evaluated with on-going yearly screening for CD, at least for the first 10 years following diagnosis of TIDM. Copyright © 2016 John Wiley & Sons.

Key words
Type 1 diabetes mellitus; coeliac disease; NICE guidelines

Introduction
Type 1 diabetes mellitus (T1DM) is a growing problem in the United Kingdom (UK). Recent data suggest that the UK has the fifth highest worldwide incidence of T1DM in children aged 0–14 years, with 24.5 per 100 000 children diagnosed with T1DM every year. This is double the rate for France or Italy. There are currently about 35 000 children and young people living with diabetes in the UK.1 Type 1 diabetes has a recognised association with other autoimmune diseases and so screening for autoimmune thyroid disease (ATD) and coeliac disease (CD) is recommended in children and young people with T1DM.2

There has been a recent review of the recommended screening procedure for CD in children with T1DM. Current updated National Institute for Health and Care Excellence (NICE) guidelines (2015) recommend screening for CD only at the time of diagnosis and thereafter only if symptoms are noted.3,4 Within the Oxfordshire Paediatric Diabetes Service, we have routinely screened yearly for CD (and for ATD). The authors have concerns that the screening approach recommended by NICE means that a significant number of diagnoses could be missed.

Aims
The aims of the study were to:
- Assess the relationship between the diagnosis of CD and T1DM in patients within our clinic population.
- Review current guidelines for screening for CD in T1DM, compare this to established regular screening for ATD, and assess this against our own screening procedures.

Methods
As part of a service evaluation in preparation for review of local guidelines we performed a cross-sectional review of the children and young people (aged 0–19 years) attending the Oxfordshire Paediatric Diabetes Service (n=342) using information contained within the Twinkle® database. Patients without T1DM were excluded. We noted the children with CD and
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ATD. Using CaseNotes® and EPR® (the trust’s electronic results system), we established the mode of diagnosis of CD and the timing of diagnosis of CD in relation to the diagnosis of T1DM. The first-line screening blood tests for CD within our trust were anti-endomysial (EMA) immunoglobulin A (IgA) antibodies, reported as either negative or positive (and further expressed as weakly positive or strongly positive) with total IgA levels. This later changed to IgA anti tissue-transglutaminase (tTG) antibodies (normal range 0–19.9 CU) with IgA levels in 2014 following a change in the immunology lab protocol. If the tTG level is positive (CU >20) then the lab will also check EMA antibodies. Patients with suspected CD from their bloods results (plus or minus positive findings in the history) would then either progress to a direct referral to the gastroenterology department where a biopsy would usually be performed, or, if the EMA/tTG antibody levels were low and in the absence of symptoms or signs, then a plan may be made to repeat the coeliac screening bloods in a few months’ time. Patient notes were reviewed if additional information was required. Patients who had a diagnosis of CD before being diagnosed with T1DM were excluded from this analysis. Microsoft Excel was used to collate all the data.

Results

Of the 342 children within the Oxfordshire Paediatric Diabetes Service, we identified 28 patients with CD (prevalence 8.2%). The M:F ratio was 1:0.8, similar to the ratio in the overall T1DM clinic population. We excluded three patients out of 28 as CD diagnosis was made before T1DM. Of the 25 remaining patients, 23 underwent a biopsy that confirmed a diagnosis of CD, one did not have a biopsy and in one, information was not available. IgA EMA/tTG antibodies were positive in 21 of the patients at diagnosis of CD, negative in one and unknown in three.

Just under one-third of the patients (28%) with T1DM and co-morbid CD were diagnosed from the initial new diabetic screening bloods done within 24 hours of T1DM diagnosis (n=7). Of the remaining 18 patients, 14 were diagnosed from annual review bloods and they had not reported any symptoms suggestive of CD. This represents 56% of the total cohort. Only one patient presented with symptoms outside annual review. Initial anti-EMA antibody screening was negative, but in view of ongoing symptoms of abdominal pain with a low haemoglobin, a biopsy was performed which confirmed CD. For three patients, details of symptomatology history and timing of coeliac screen bloods were unobtainable (Figure 1).

When we looked at the timing of CD from the onset of T1DM, while the majority of the 25 patients analysed were diagnosed with CD within the first year of T1DM diagnosis (44%, n=11), another 44% were diagnosed after two years and 12% after five years with T1DM (n=1, 5–10 years; and n=2, >10 years). (Figure 2.)

Of the 342 patients within the clinic, 20 were identified as diagnosed with ATD. This represents 5.8% of the clinic population with a female preponderance (M:F ratio = 1:6) as seen in the general population of ATD.

Discussion

Type 1 diabetes mellitus is a growing problem in the UK and worldwide, and therefore it will become increasingly important to understand the risk of associated diseases such as CD and ATD.

Coeliac disease has significant effects on the health of children and young people such as growth failure, pubertal abnormalities, weight loss, osteopenia, osteoporosis, anaemia, neurological disorders, or increased risk of lymphoma. However, one study has suggested that those with both T1DM and CD have a milder phenotype with fewer complications of CD. Some studies show an effect on glycaemic control but this is controversial; variable effects on glycosylated haemoglobin (HbA1c) have been identified, and Mohn et al. have reported that CD may cause episodes of unexplained hypoglycaemia.

Hypothyroidism does not usually affect glycaemic control, but patients may have lower insulin requirements, and this is postulated to be due to reduced insulin degradation. Hyperthyroidism can present as...
Previous literature suggests that CD is significantly less prevalent than ATD in T1DM. Studies from the UK suggest a prevalence of 4.4–5.8% of CD in children and young people with T1DM, and the worldwide prevalence varies between 1–16%, but it is recognised that there is a higher prevalence than in the general population (0.2–5.5%). There is also some evidence suggesting an increasing prevalence of CD in T1DM since the mid-1990s, and this increase has also been seen in the non-diabetic population.

Autoimmune thyroid disease has historically been the most common autoimmune disorder reported in T1DM with thyroid autoantibodies detected in 12.1–23.4% of children and young people with T1DM and clinical hypothyroidism quoted at 4–18% (cf. general population 5–10%). Hyperthyroidism in T1DM is much less common, with a prevalence rate of 1.5–4.4%.

Our centre has historically performed yearly screening for both ATD and CD. The results above show a prevalence of CD of 8.2% in our clinic population which is higher than the prevalence of ATD in our population (5.8%) and also higher than most published figures of CD in T1DM. The authors believe that the higher detection rate of CD in our population is related to our rigorous screening procedures. We suggest that the generally lower prevalence of CD in T1DM reported in the literature is linked to the limited screening for CD.

NICE guidelines, recently updated in September 2015, recommend an initial screen for CD at diagnosis of T1DM. IgA anti-tTG antibodies and total IgA levels are advised as first-line screening tests. If these are positive, the patient should then be referred for further tests such as anti-EMA antibodies, HLA genotyping or directly for intestinal biopsy. However, if the initial antibody tests are negative, the guidelines only recommend further screening if the patient becomes symptomatic.

A number of alternative guidelines do recognise that there is an increased incidence of CD in the first five years after diagnosis of T1DM, and therefore advocate more regular screening within those initial five years. The 2009 guidelines from the International Society for Pediatric and Adolescent Diabetes (ISPAD) recommend screening annually for the first five years following the diagnosis and then every two years following that.

Most guidelines rely on serological tests, usually anti-tTG, as the first-line screening tool. The European Society for Paediatric Gastroenterology, Hepatology and Nutrition produced guidelines in 2012 which suggest that HLA genotyping should be used first line as a screening for those at higher risk of developing CD. However, very few centres in the UK have implemented these guidelines. A recent study of HLA genotyping in a Scottish cohort has shown that a very high percentage of children with T1DM will possess the ‘risk’ haplotypes for CD. Ninety-four percent of their cohort were positive for one or both HLA of DQ2/DQ8. Therefore, they felt that HLA genotyping was likely not beneficial or cost-effective as a screening test.

Perhaps in view of the perceived higher prevalence of ATD in T1DM most guidelines have suggested frequent, on-going screening for ATD in T1DM. The 2015 NICE guidelines suggest screening for ATD at diagnosis of T1DM and then annual screening until transition to adult services.

Similarly, ISPAD, American Diabetes Association and Australasian Paediatric Endocrine Group guidelines recommend screening either annually or every two years.

The authors have concerns that the current NICE guidelines for CD screening in T1DM could miss a significant number of patients. In the results above, 56% (n=14) of those with CD were identified on annual review bloods, with no prior symptoms of the disease. Common symptoms of CD include malabsorption which can result in flatulence, bloating, diarrhoea and weight loss. Other symptoms can include anaemia, irritability, fatigue or depression. In many cases of undiagnosed CD, however, there are no symptoms at all.

Previous literature has shown that the symptoms of CD can be subtle and easy to miss and many patients have initially negative screening tests. Therefore, our concern is that many patients will be missed, or only identified after significant impact on their health, if regular screening is not implemented.

In addition to the symptoms related to malabsorption mentioned above, CD can result in serious nutrient deficiencies of the fat-soluble vitamins A, D, E, and K, and of vitamin B12 and folate, iron and calcium. In children, this can lead to delayed growth or short stature as well as delayed puberty – all of which can add to the burden of T1DM.

Specifically in persons with T1DM, malabsorption of nutrients from undiagnosed/untreated CD can lead to frequent, unexplained low or high blood glucose readings. Long-term complications of untreated CD include fertility problems, benign or malignant tumours of the small intestine and osteoporosis. At a cost of £215–20.00 per test for the IgA anti-tTG antibody test we believe this is a cost-effective screening test which can help pick up cases in what is in the majority of cases an asymptomatic, but clinically significant, illness.

Our results do show the highest incidence of CD diagnosis in the first year after diagnosis of T1DM. However, there were still a number identified five years post-T1DM diagnosis (12%, n=5). The recent meta-analysis by Pham-Short et al. also showed delayed diagnosis of CD. Seventy-nine percent were diagnosed in the first five years with the highest incidence in the first year; however, 16% were only diagnosed after the first five years and 5% over 10 years after the diagnosis of T1DM. The results from our study and the previous meta-analysis suggest that not only should regular screening of CD be implemented, but that it should continue for many years following the diagnosis of T1DM.

Conclusion

Coeliac disease and ATD can have a significant impact on the wellbeing and health of children with T1DM. Previous literature has suggested that CD is less commonly associated

unexplained difficulty in maintaining glycaemic control, increased insulin requirements, can precipitate diabetic ketoacidosis, and in some instances has been related to atrial fibrillation/cardiac arrest.

Many cases of undiagnosed CD have initially negative screening tests. Therefore, our concern is that many patients will be missed, or only identified after significant impact on their health, if regular screening is not implemented.

In addition to the symptoms related to malabsorption mentioned above, CD can result in serious nutrient deficiencies of the fat-soluble vitamins A, D, E, and K, and of vitamin B12 and folate, iron and calcium. In children, this can lead to delayed growth or short stature as well as delayed puberty – all of which can add to the burden of T1DM.

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Conclusion

Coeliac disease and ATD can have a significant impact on the wellbeing and health of children with T1DM. Previous literature has suggested that CD is less commonly associated
with T1DM than ATD and this appears to be reflected in the current NICE guidelines. Other international screening guidelines are variable, but the NICE guidelines updated in 2015 suggest screening for CD only at diagnosis, and thereafter only if the patient has signs or symptoms suggestive of CD. This is in contrast to the recommended annual screening for ATD.

The CD prevalence of 8.2% in our clinic population is higher than in other UK studies (including the National Paediatric Diabetes Audit 2014–15 data which quote CD levels of 4.7% in children and young people with T1DM for England and Wales) and particularly high in contrast to the prevalence of ATD at only 5.8%. The majority of cases were asymptomatic and identified by annual review bloods, after initially negative screening tests.

Literature shows that CD can largely be a silent disorder, with many patients not having symptoms prior to diagnosis. Untreated, long-term CD can have, however, in significant health complications.

With the prevalence of CD on the increase, and studies showing a significant number of new cases being diagnosed five or more years after the diagnosis of T1DM, we suggest that national screening guidelines should be re-evaluated.

We recommend increased screening for CD in patients with T1DM. This should be yearly from the time of diagnosis and on-going, or at least yearly for the first 10 years after diagnosis of T1DM. We welcome and encourage further debate on this issue.

Declaration of interests

There are no conflicts of interest declared.

References


Key points

● The prevalence of coeliac disease in children with type 1 diabetes mellitus may be higher than previously thought.
● The majority of cases of coeliac disease in type 1 diabetes mellitus are asymptomatic and have initially negative screening tests, so would be missed on current National Institute for Health and Care Excellence screening procedures.
● We recommend yearly screening for coeliac disease in children and young people with type 1 diabetes mellitus.

If you would like to comment on this article or discuss your current practice on this topic, Practical Diabetes would be pleased to hear from you. Please email the Managing Editor, Helen Tupsy: email htupsy@wiley.com, with your comments.

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