Coeliac disease and type 1 diabetes mellitus: An important association

Geoffrey Holmes

Coeliac disease and type 1 diabetes are frequently associated. Diarrhoea, malabsorption, unstable glycaemic control and growth failure indicate the possible presence of coeliac disease; however, many individuals have subtle complaints that do not immediately suggest the diagnosis, including tiredness, lack of well-being and mild abdominal upsets. Some people even regard themselves as asymptomatic and only recognise symptoms in retrospect and following the benefits conferred by a gluten-free diet. This article describes the clinical aspects of coeliac disease in type 1 diabetes, the effects of treatment with a gluten-free diet and guidelines for screening and monitoring the condition.

Coeliac disease results from an abnormal reaction to dietary gluten, a protein complex found in wheat, rye and barley cereals. It occurs worldwide in genetically predisposed individuals, who develop immune-mediated damage to the lining of the upper small intestine, whereby the villi become damaged and the surface flattened, resulting in a reduced surface area for absorption. This leads to malabsorption of nutrients and ill health in most individuals, although some can have mild or even no symptoms (van Heel and West, 2006). Children and adults traditionally present with the "classic symptoms" of weight loss, diarrhoea and fatty stools, which are indicative of malabsorption; however, nowadays, most present with non-classic symptoms such as fatigue; dyspepsia; vague abdominal pain and bloating suggestive of irritable bowel syndrome; constipation; and features such as growth failure, anaemia, mouth ulcers, osteoporosis and neuropathy (Schuppan and Zimmer, 2013). Very subtle disturbances, such as deterioration in school performance, irritability and short temperedness, can also be presenting features (Holmes, 2002). This clinical diversity often delays or obscures the diagnosis. Furthermore, some individuals are asymptomatic and are only picked up by screening at-risk groups, such as first-degree relatives of people with coeliac disease and people with immune disorders.

While coeliac disease was once considered a disorder of childhood, about a third of cases are now diagnosed in people over the age of 60 years. The development of reliable screening tests in the last few years that rely on the detection of antibodies against endomysium and tissue transglutaminase type 2 (TG2) has shown that coeliac disease is a common, life-long disorder with a serological prevalence in the UK of about 1% (West et al, 2003). However, not all of these cases are diagnosed, and this has given rise to the concept of the "coeliac iceberg," reflecting the fact that the majority of people remain "below the surface," undiagnosed (Holmes et al, 2009). The challenge for healthcare workers is to identify these undiagnosed individuals and offer them a gluten-free diet that will restore the majority to full health and may prevent the development of complications such as osteoporosis and lymphoma (Lewis and Holmes, 2010).

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Article points

1. Coeliac disease and type 1 diabetes are frequently associated; however, the former remains underdiagnosed as many individuals do not present with the classic signs and symptoms.
2. A screening programme to detect coeliac disease is preferable to a case-finding strategy so that all people, whether they have the classic symptoms or not, are detected and receive treatment to improve health and reduce the risk of complications such as osteoporosis and lymphoma.
3. All people should be offered a gluten-free diet and should be introduced to a skilled dietitian. Those who do not want to undergo the diet should be monitored and prompt action taken if features of coeliac disease arise in the future.

Key words

- Coeliac disease
- Type 1 diabetes

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1. Type 1 diabetes and coeliac disease appear to be associated, with the prevalence of the latter estimated to be 4.5% in children with type 1 diabetes. Similarly, people with coeliac disease have a two- to three-fold increased risk of developing type 1 diabetes.
2. The symptoms of coeliac disease in people with type 1 diabetes can vary and often go unnoticed until a gluten-free diet is started; however, common symptoms include gastrointestinal problems, weight loss and growth retardation.
3. There is some evidence that coeliac disease can impair glycaemic control, probably as a result of malabsorption in the intestine, and it can also be a risk factor for diabetic retinopathy.

Coeliac disease associated with type 1 diabetes

It follows that, because coeliac disease is so common, other disorders will occur in association (Lewis and Holmes, 2010). Frequently, these will be coincidental happenings but in some instances they occur more often than by chance. Recent studies have demonstrated an increased prevalence of coeliac disease in some autoimmune disorders, including type 1 diabetes, thyroid disease and liver disorders. Type 2 diabetes, which typically occurs in an older age group, is no more common in people with coeliac disease than in the general population, and may even be less common (Kabbani et al, 2013), and will not be considered further in this article.

Type 1 diabetes is the most common and best researched association with coeliac disease and precedes the diagnosis of the latter in about 90% of cases (Pocecco and Ventura, 1995). An analysis of 26 screening studies has shown that the average prevalence of coeliac disease among children with type 1 diabetes is around 4.5% (Holmes, 2002). In case series of children from Saudi Arabia (Al-Hussaini et al, 2012) and Sweden (Bybrant et al, 2014), figures of 11.3% and 9.1%, respectively, were reported. In adults, the average prevalence in eight studies was 3.4% (Holmes, 2001). In a recent meta-analysis of 27 studies published between 2000 and 2014, including 26 605 adults and children with type 1 diabetes, 6% of the participants had biopsy-proven coeliac disease (Elfström et al, 2014).

Similarly, before the age of 20 years, people with established coeliac disease have a two- to three-fold increased risk of developing type 1 diabetes (Ludvigsson et al, 2006). The risk of having the two diseases together is three times higher in children who are diagnosed with type 1 diabetes aged <4 years than in those diagnosed aged >9 years (Cerutti et al, 2004).

It is not surprising that these disorders are connected, because both are linked not only to the human leukocyte antigen (HLA)-DQ2 and HLA-DQ8 haplotypes but also to non-HLA loci (Smyth et al, 2008). The link between type 1 diabetes, coeliac disease and gluten is complex. Gluten may gain access to the immune system in diabetes because of increased permeability, as occurs in coeliac disease (Heyman et al, 2012). It has been demonstrated that some children with diabetes have anti-TG2 antibodies in the small intestinal mucosa, suggesting that these children are sensitive to gluten (Maglio et al, 2009). These observations raise the intriguing possibility that gluten might be of aetiological importance in type 1 diabetes.

Clinical aspects

Reports on the clinical aspects of type 1 diabetes associated with coeliac disease and the effects of a gluten-free diet on outcomes, such as glycaemic control and diabetes complications, often give conflicting results. This may be because small numbers of people with diabetes and coeliac disease and controls were included in some investigations, and it is difficult to draw valid conclusions. Furthermore, in assessing the effects of a gluten-free diet, establishing how strictly people adhere to the diet can be difficult. While authors usually draw attention to these shortcomings, research papers should be read with these considerations in mind.

The proportion of people with symptoms and signs varies across reports. As more recent studies illustrate, these differences almost certainly reflect how carefully the signs and symptoms were sought. In one study, out of 33 children with diabetes and coeliac disease, all interviewed by doctors, 28 (85%) had symptoms or biochemical features of coeliac disease, and in four the symptoms were only recognised retrospectively after the introduction of a gluten-free diet (Hansen et al, 2006). Narula et al (2009) found that 13 of 17 children (76%) had gastrointestinal signs, whereas Taler et al (2012) found that 18 of 68 (26%) had symptoms including growth retardation, weight loss, failure to gain weight and gastrointestinal problems.

Similar (Narula et al, 2009) and worse (Leeds et al, 2011) levels of glycaemic control have been reported in people with type 1 diabetes and coeliac disease compared to those with diabetes alone. Worse control might be anticipated in light of malabsorption from a damaged bowel, which may vary from day to day. A higher prevalence of retinopathy in people with type 1 diabetes and coeliac disease compared with controls has also been observed (Leeds et al, 2011). A diagnosis of coeliac disease for >10 years was found to be a risk factor for retinopathy in people with type 1 diabetes (Mollazadegan et al, 2013). However, another study showed a lower risk of retinopathy in people with

the two conditions compared to those with diabetes alone (Bakker et al, 2013a). People with type 1 diabetes and coeliac disease have a greater carotid intima–media thickness than those with either diabetes or coeliac disease alone, and this could be of importance in accelerating cardiovascular disease (Pitocco et al, 2011).

Gopee et al (2013) compared the levels of albuminuria (a marker of renal function) in 24 children with type 1 diabetes and biopsy-proven coeliac disease on a gluten-free diet for at least 1 year, 55 with type 1 diabetes alone (matched for age, gender, diabetes duration and glycaemic control), and 22 age- and gender-matched children without diabetes. None of those with coeliac disease had persisting anti-TG2 antibodies, which indicated good compliance with the diet. It was found that those children with type 1 diabetes and coeliac disease had lower levels of albumin in their urine than those with diabetes alone. After a median follow-up of 5 years, albuminuria progression was only seen in participants with diabetes alone, not those with both conditions. These observations indicate that coeliac disease and/or its management with a gluten-free diet protects the kidneys from damage in children with diabetes. One mechanism for this might be a change in protein intake as a result of ingesting a gluten-free diet. Another study showed that non-adherence to a gluten-free diet was associated with early elevation of albumin excretion rate, a risk factor for the development of renal disease (Pham-Short et al, 2014). In combination, these studies support the need to advise strict adherence to a gluten-free diet in this population.

People with coeliac disease and type 1 diabetes are prone to depression, with 37% affected compared to 16% with coeliac disease alone (Garud et al, 2009). It appears that having two chronic diseases is sufficient to tip the balance towards depression. Such individuals may also have a reduced quality of life, particularly with regard to social functioning (Bakker et al, 2013b). These problems can be alleviated by skilled and sympathetic healthcare providers.

Effects of a gluten-free diet

Reports of the effects of a gluten-free diet in people with type 1 diabetes and coeliac disease are conflicting, as can be seen in *Table 1*. These disparate findings may be a result of the small numbers of patients and controls studied, along with variable adherence of individuals to a gluten-free diet. In addition, people with coeliac disease form a heterogeneous group, with some having classical symptoms, others having non-classical symptoms and others being asymptomatic; all this can make assessment of treatment difficult.

Table 1. Results of studies on the effects of a gluten-free diet in people with type 1 diabetes and coeliac disease.

Study	Results			
	Clinical improvement	Height/weight gain	Improvement in HbA_{1c}	Improvement in hypoglycaemia
Acerini et al (1998)	✓	✗	✗	✗
Kaukinen et al (1999)			✗	✗
Westman et al (1999)		✗		
Mohn et al (2001)			✗	✓
Amin et al (2002)	✓	✓	✓	
Saadah et al (2004)		✓	✗	
Sanchez-Albisua et al (2005)	✓	✓	✓	
Hansen et al (2006)	✓	✓	✗	✓
Narula et al (2009)	✓	✓		
Fröhlich-Reiterer et al (2011)		✓		
Pham-Short et al (2014)			✓	

In recent years, the quality and variety of gluten-free foods has improved enormously, but people do find that the diet impedes their enjoyment of food, is expensive (although some gluten-free foods are available on prescription) and restricts activities such as eating out and social interaction (Whitaker et al, 2009).

Should asymptomatic people with coeliac disease and type 1 diabetes be treated with a gluten-free diet? Asymptomatic people may in fact be unusual if careful screening takes place; Saadah et al (2004) found that 95% of their participants had symptoms at presentation. As already mentioned, it is important that healthcare practitioners take a

Page points

1. All people with coeliac disease and type 1 diabetes should be offered a gluten-free diet, as this can prevent complications such as osteoporosis.
2. In addition to regular monitoring of their diabetes, people with the two conditions should be followed up annually to check growth and development (in children), health status and compliance with a gluten-free diet, and indices such as haemoglobin, folate, iron, calcium and anti-tissue transglutaminase antibody levels. Scans for osteoporosis may also be required.
3. Many clinicians favour screening for coeliac disease in people with type 1 diabetes, given the association between the two conditions, the availability of reliable screening tests and the fact that intervention with a gluten-free diet can improve health and reduce the risk of complications.

careful medical history and be aware of the subtle ways that people may present, as such individuals may benefit from a gluten-free diet (Holmes, 2002). It would seem prudent to offer all people with type 1 diabetes who are diagnosed with coeliac disease a gluten-free diet, with careful follow-up to check their progress. Those who improve will want to continue with the diet, while those who perceive no benefit are likely to abandon it; these individuals should be made fully aware that a gluten-free diet can prevent complications such as osteoporosis and lymphoma (Lewis and Holmes, 2010).

As well as being introduced to a dietitian skilled in the gluten-free diet, all people should be encouraged to join Coeliac UK (available at: www.coeliac.org.uk), a self-help society that provides a regularly updated Food and Drink Directory of gluten-free products and other literature, and which holds national and local meetings to help individuals adjust to the diet.

Follow-up

People with coeliac disease should be followed up for life, either in a specialist clinic or by a family doctor with a particular interest in the condition; otherwise, they are more likely to stray from the gluten-free diet and have poor health. As the number of diagnoses is increasing dramatically (West et al, 2014), other models of care are being looked at, such as dietitian- or nurse-led clinics, as well as telephone interviews so that attendance at clinics can be avoided for people who do not report any problems with their health or with diet compliance.

For those who wish to attend clinics for follow-up, an annual review is usual, in which weight in adults and growth and development in children can be monitored and the status of health and compliance with a gluten-free diet checked, aided by blood tests to determine indices such as haemoglobin, folate, iron, calcium and anti-TG2 antibody levels. Scans for osteoporosis may also be required. Membership of Coeliac UK should be confirmed. Individuals who are unwell or are having difficulties with the diet should have access to care at any time.

Although a gluten-free diet restores most people to full health, with restoration of small bowel mucosal architecture (Schuppan and Zimmer, 2013), occasionally the expected responses do not occur or are lost, and people deteriorate again. If these individuals are not becoming unwell through gluten consumption, other tests, including small bowel imaging and repeat small bowel biopsies, require consideration to look for complications of coeliac disease such as intestinal ulcerations, small bowel carcinomas and lymphomas (Catassi et al, 2005; Lewis and Holmes, 2010).

People with both coeliac disease and type 1 diabetes should have access to the care for coeliac disease outlined above but will also require long-term care for diabetes, with blood glucose monitoring and checks for diabetes complications.

People who are diagnosed with these conditions in childhood or adolescence should be referred to an adult service at an appropriate age, usually the mid teens, for continuing care.

Screening

It is easy to make a case for screening coeliac disease in people with type 1 diabetes given the high frequency of the association, the availability of reliable screening tests and the fact that intervention with a gluten-free diet can improve health and avoid complications. NICE (2004) guidelines recommend that people with type 1 diabetes be screened for coeliac disease; however, there is no consensus in the many guidelines that have been published over the last decade as to how this should be carried out with regard to, for example, frequency of screening, which tests to use and whether to consider only those individuals who have symptoms (Simpson et al, 2013; Porter et al, 2014). Furthermore, it is not certain how long to screen for. In one study, 48 of 77 children (62%) with type 1 diabetes who were diagnosed with coeliac disease had developed antibodies within 2 years of the diagnosis of diabetes, indicating the importance of screening during the early years following diabetes diagnosis (Bybrant et al, 2014). However, although the mean time to coeliac diagnosis was 2.4 years, the range was 0.12–12.5 years, showing that new cases of coeliac disease can be detected after many years of screening.

All this reflects a poor evidence base on which to anchor firm recommendations, although future research is likely to correct this unsatisfactory situation. Despite the uncertainty, many clinicians favour screening. A survey of the approach to

screening by 34 consultant paediatricians and physicians who cared for people aged <15 years with type 1 diabetes in New Zealand revealed a wide variation in practice (Porter et al, 2014). Twenty-one used a departmental protocol and 25 screened at the diagnosis of diabetes. All used anti-TG2 antibody assays and some tested for anti-endomyseal antibodies in addition. Twenty-one of the respondents who were screened at diagnosis were then screened every 2–3 years. Those who did not regularly screen were usually triggered to re-screen by the appearance of symptoms. Thirty-two of the clinicians only commenced a gluten-free diet in people with biopsy-proven coeliac disease.

Screening practices for coeliac disease in type 1 diabetes were determined in the US and Canada by sending questionnaires to dietitians and diabetes educators (Simpson et al, 2013). The results showed that only a minority of centres screened and there was no consistency in practice. Of the 514 responders, 35% reported that they performed screening. Of these, 60% only screened people with symptoms and there was no uniformity as to how frequently screening was subsequently carried out.

The European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN), in guidelines for the diagnosis of coeliac disease published in 2012, presented a scheme for the diagnosis of coeliac disease in people with type 1 diabetes (Husby et al, 2012). The initial action recommended is to test people for HLA-DQ2 and HLA-DQ8. People without these genotypes are very unlikely to develop coeliac disease and require no further consideration. If HLA status cannot be determined, people should have their total immunoglobulin A levels measured and tested for anti-TG2 antibodies, as with people who test positive for the HLA markers. Those with antibody levels greater than three times the upper limit of normal should be referred for duodenal biopsy. Those who test negative for these antibodies may still develop coeliac disease and, although there is no firm evidence, it was recommended that children be tested every 2–3 years.

If anti-TG2 antibodies are present but at low levels – less than three times the upper limit of normal – then a false-positive result is possible. In this situation, an anti-endomysial antibody test may be positive and increases the likelihood of coeliac disease being present, and should lead to duodenal biopsy. If the endomysial antibody test is negative, individuals should be followed up whilst on a normal diet every 3–6 months until anti-TG2 levels either become normal or increase to levels at which endoscopy is indicated. If coeliac disease cannot be conclusively proved in a seropositive patient, a normal diet should be continued, with re-evaluation at regular intervals. Since people with diabetes usually undergo long-term follow-up, there should be no difficulty in screening for coeliac disease annually or as clinical features dictate. A helpful algorithm is published in the ESPGHAN guidelines that sets out the above strategy for diagnosing coeliac disease in type 1 diabetes (Husby et al, 2012). However, centres that undertake screening may modify these to suit local circumstances.

It is important to be aware that a number of kits are available to measure anti-TG2 antibody levels, some of which do not perform to a high standard (Hill et al, 2014). Laboratories should only use assays that have good analytical and diagnostic performance.

When a study was undertaken to determine how well these recommendations were being adhered to, wide variation was observed among paediatricians (Atherton et al, 2014). Only 12% of paediatricians from 17 centres in the UK determined HLA status and only 35% would subsequently test HLA-positive patients who were asymptomatic. Surprisingly, only 82% would retest symptomatic children. When five clinical scenarios were given to clinicians, a wide variety of different management opinions were given. It was concluded that even paediatric gastroenterologists had a lack of understanding about how to interpret test results and that further education was urgently required.

Conclusion

While there is much to unravel, enough is already known to guide healthcare providers in the diagnosis and management of people with associated coeliac disease and type 1 diabetes. It is incumbent on practitioners to be aware of the association so that patients receive optimal care and enjoy good health. The recent ESPGHAN guidelines provide a useful algorithm to help healthcare providers in these circumstances. ■

Page points

1. The European Society for Pediatric Gastroenterology, Hepatology and Nutrition have produced a helpful algorithm for the diagnosis of coeliac disease in people with type 1 diabetes.
2. The core of screening is testing for the human leukocyte antigen (HLA)-DQ2 and HLA-DQ8 haplotypes, followed by tests for anti-tissue transglutaminase type 2 (anti-TG2) antibodies. Diagnosis is confirmed with duodenal biopsy.
3. People who have low, but present, anti-TG2 levels can also be tested for anti-endomysial antibodies. If this test is negative, the individual should be followed up whilst on a normal diet every 3–6 months until anti-TG2 levels either become normal or increase to levels at which biopsy is indicated.

"While there is much to unravel, enough is already known to guide healthcare providers in the diagnosis and management of people with associated coeliac disease and type 1 diabetes. It is incumbent on practitioners to be aware of the association so that patients receive optimal care and enjoy good health."

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