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Coeliac disease: a diverse clinical syndrome caused by intolerance of wheat, barley and rye

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Coeliac disease is a lifelong intolerance to the gluten found in wheat, barley and rye, and some patients are also sensitive to oats. The disease is genetically determined, with 10% of the first-degree relatives affected and 75% of monozygotic twins being concordant. Of the patients with coeliac disease 95% are human leucocyte antigen (HLA)-DQ2 or HLA-DQ8 positive. Characteristically, the jejunal mucosa becomes damaged by a T-cell-mediated autoimmune response that is thought to be initiated by a 33-mer peptide fragment in A2 gliadin, and patients with this disorder have raised levels of anti-endomysium and tissue transglutaminase antibodies in their blood. Coeliac disease is the major diagnosable food intolerance and, with the advent of a simple blood test for case finding, prevalence rates are thought to be approximately 1:100. Classically, the condition presented with malabsorption and failure to thrive in infancy, but this picture has now been overtaken by the much more common presentation in adults, usually with non-specific symptoms such as tiredness and anaemia, disturbance in bowel habit or following low-impact bone fractures. Small intestinal biopsy is necessary for diagnosis and shows a characteristically flat appearance with crypt hypoplasia and infiltration of the epithelium with lymphocytes. Diet is the key to management and a gluten-free diet effectively cures the condition. However, this commitment is lifelong and many aisles in the supermarket are effectively closed to individuals with coeliac disease. Compliance can be monitored by measuring antibodies in blood, which revert to negative after 6–9 months. Patients with minor symptoms, who are found incidentally to have coeliac disease, often ask whether it is necessary to adhere to the diet. Current advice is that dietary adherence is necessary to avoid the long-term complications, which are, principally, osteoporosis and small bowel lymphoma. However, risk of these complications diminishes very considerably in patients who are on a gluten-free diet.

Coeliac disease: Gluten: Diet

Coeliac disease (CD) is a genetically-determined autoimmune condition that can present at any age and for which there is a clearly-defined pathology and diagnostic test. CD is a permanent intolerance to the gliadin fraction of proteins in wheat, barley and rye, with some individuals with CD also sensitive to oats. Although primarily manifest as a disorder of the mucosa of the duodenum and jejunum, leading in severe cases to malabsorption, it can present in many ways and is a syndrome with many facets. Increasingly, cases are found as a result of screening blood tests in anaemic patients or in associated conditions such as type 1 diabetes, thyroid disease or from endoscopic biopsies of the duodenum in procedures carried out for unrelated conditions such as dyspepsia or gastro-oesophageal reflux disease. This so-called 'silent' CD is but one aspect of a condition that can include: anaemia; osteoporosis; dermatitis herpetiformis (DH; a skin manifestation of an autoimmune response associated with CD); microscopic colitis; frank malabsorption with weight loss and steatorrhoea; infertility; miscarriage; folate deficiency; malignancy such as lymphoma; rare neurological disorders. CD, and most of its manifestations, is entirely

Abbreviations: AGA, anti-gliadin antibodies; BMD, bone mineral density; CD, coeliac disease; DH, dermatitis herpetiformis; EMA, endomysial antibodies; GFD, gluten-free diet; HLA, human leucocyte antigen; tTG, tissue transglutaminase.

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Table 1. Presenting features of coeliac disease

Adults:
Diarrhoea, altered bowel habit
Abdominal pain, dyspepsia, bloating
Aphthous ulcers
Anaemia (Fe or folate and rarely vitamin B_{12})
Weight loss
Dermatitis herpetiformis
Malabsorption, oedema
Osteoporosis, low impact fracture
Infants and children:
Loss of appetite, failure to thrive, miserable child
Malabsorption, diarrhoea, abdominal distension
Small stature, muscle wasting
Less common symptoms:
Tiredness, depression, muscle weakness, amenorrhea, bone pain, infertility
No specific symptoms:
Seroprevalence studies in health populations
Family history
Screening in associated conditions (see Table 4)
Biopsy during endoscopy for unrelated symptoms

treatable by diet. The development in recent years of simple but reliable blood tests to identify CD has led to a great increase in coeliac awareness and understanding of the condition. CD is a subject of substantial research in many countries, and approximately 700–800 papers on this topic appear annually. The present review will focus on current thinking about CD, particularly from the clinical, nutritional and dietetic perspective. There are a number of recent comprehensive reviews that cover other aspects of the condition (Ciclitira, 2001; Green & Jabri, 2003; Mowat, 2003; Treem, 2004; Alaedini & Green, 2005; James, 2005).

Symptoms and clinical manifestations

Although the diagnosis of CD is reached by many routes, there are some key symptoms or clinical findings that should always raise the possibility of this condition (Table 1). Diarrhoea is the commonest symptom, although its prevalence has diminished in recent years from 73% of patients to 43% of patients (Lo *et al*. 2003), probably because of the increasing numbers diagnosed after screening. Associated with diarrhoea can be abdominal pain, wind and weight loss. Frank steatorrhoea is now rare. In children gastrointestinal symptoms are also a common presenting feature and often go with anorexia and failure to thrive, short stature and, again rarely, the pot-bellied wasted miserable child (Rawashdeh *et al*. 1996). Other gastrointestinal symptoms include constipation, vomiting, dyspepsia and mouth ulcers. The onset of CD is triggered by weaning in children (Norris *et al*. 2005), and in adults it can appear to follow a gastrointestinal infection, pregnancy or even surgery. Other features include Fe or folate deficiency, anaemia, aphthous ulcers or the rash of DH (Bottaro *et al*. 1999; Feighery, 1999; Hin *et al*. 1999; Green *et al*. 2001; Tursi *et al*. 2001; Gillett *et al*. 2003; Lo *et al*. 2003; Elsurer *et al*. 2005).

However, increasingly commonly, CD is diagnosed after screening of asymptomatic populations such as blood donors, first-degree relatives, at-risk groups with type 1 diabetes, thyroid disease, osteoporosis or microscopic colitis and incidentally at gut biopsy. In these subclinical or 'silent' versions of CD Fe-deficiency anaemia is a much commoner feature (Bottaro *et al*. 1999; Hin *et al*. 1999; Tursi *et al*. 2001; West *et al*. 2003*a*). Once the likelihood of CD has been raised, patients report minor symptoms that they have had for years such as tiredness, sore mouth, hair loss, abdominal discomfort, wind or abnormal bowel habit, which had previously been taken for granted. Treatment in these cases can often result in marked and unexpected improvements in health.

CD may, therefore, present with almost any symptoms and to any branch of medical practice. The most important step in diagnosis is awareness of its diverse manifestations.

Genetics and pathogenesis

The pathology of CD is that of a T-cell-mediated autoimmune disorder, triggered by certain cereal proteins, that affects principally the duodenum and upper jejunum. The normal small bowel mucosa is covered in fine finger-like projections or villi sitting on top of a thin layer of muscle, the muscularis mucosa, and connective tissue stroma, the lamina propria. The villi are covered in a single layer of epithelial cells that originate in crypts at the base of the villi and play a crucial role in digestion and absorption. Each epithelial cell is covered in microvilli. Villus height:crypt depth is usually $\geq 3:1$ in healthy adults.

In CD there is complete loss of villi and hypertrophy of the mucosa with infiltration of the lamina propria by inflammatory cells (lymphocytes, plasma cells, eosinophils and mast cells), which results in the so-called flat mucosa characteristic of the condition. A key feature is a migration of lymphocytes to the surface epithelium (intra-epithelial lymphocytes). Intra-epithelial lymphocytes can be found throughout the gut in CD, right down to the rectum, and are the earliest changes to be seen. Varying extents of severity are reported (Marsh, 1992; Whitehead, 1995).

Three factors are essential in relation to the series of events that lead to these pathological changes: genetic susceptibility; the immune system; gluten in the diet. There is a strong genetic component to CD. Concordance is 75–90% in monozytotic twins and 10–20% in dizygotic twins. In first-degree relatives the prevalence is 10% and in second-degree relatives it is 2%. Almost all patients with CD (95%) carry the human leucocyte antigen (HLA)-DRB1*03 (HLA-DQ2 or HLA-DRB*04 DQ8) haplotypes on chromosome 7. Concordance amongst HLA-identical siblings is about 30% (Auricchio *et al*. 1999; Greco *et al*. 2002; Fasano *et al*. 2003; Maki *et al*. 2003). Other candidate genes may also be involved (Van Belzen *et al*. 2003; Diosdado *et al*. 2004).

Gluten is a water-soluble protein found in wheat. It consists of an alcohol-soluble fraction, gliadin, and an insoluble fraction, glutenin. The gliadin fraction can be further subdivided into α, β, γ and ω fractions, all of which

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are toxic in CD, although the α fraction is thought to be the most active. These alcohol-soluble proteins are known as prolamins and are termed gliadin in wheat, hordein in barley, secalin in rye and avenin in oats. A 33-mer peptide, rich in proline and glutamine, has been isolated from gliadin and is thought to contain the toxic sequence (Shan *et al*. 2002). After digestion of wheat proteins, or barley or rye proteins, by pancreatic enzymes this 33-mer peptide survives, possibly because of the high proline content. It also resists digestion by the brush border and can cross the epithelial cell membrane and pass into the cytosol (Matysiak-Budnik *et al*. 2003).

This glutamine-rich peptide is then deamidated by transglutaminase enzymes (Skovbjerg *et al*. 2004). The deamidated epitope cross-links and has a high affinity to the HLA-DQ2 molecule, which is then presented to CD4+ T-cells. These T-cells become activated and secrete inflammatory cytokines etc. (Mowat, 2003), and tissue damage occurs. T-cell lines from patients with CD also recognise peptide sequences from barley and rye but not oats (Vader *et al*. 2003). These changes start to occur within 4–6 h of exposure to the toxic peptide (Fraser *et al*. 2003).

Serology and diagnosis

A number of serological tests have been developed over the years (see Dahele & Ghosh, 2000), including anti-reticulin antibodies (now obsolete), anti-gliadin antibodies (AGA; the main serological CD test for many years following its introduction in 1958), endomysial antibodies (EMA; endomysium is a connective tissue protein) and, mostly recently, antibodies to tissue transglutaminase (tTG). Both IgA and IgG AGA antibodies are present in the sera of patients with CD, although they are not specific because gliadin crosses the normal gut mucosa, and approximately 5–10% of the healthy population will be positive for gliadin antibodies, particularly older individuals. It has been suggested (Dahele & Ghosh, 2000) that AGA positivity in otherwise healthy individuals may be associated with minor abnormalities on biopsy, but this response may just represent increased sensitivity to other factors such as non-steroidal anti-inflammatory drugs. Both IgG and IgA AGA are measured, with IgG showing reasonable sensitivity but poor specificity whilst IgA AGA has better specificity but poor sensitivity (Berger & Schmidt, 1996; Chartrand *et al*. 1997; Dahele & Ghosh, 2000).

EMA were first described in CD about 20 years ago (Chorzelski *et al*. 1984) and rapidly replaced AGA as the serological test of choice because of their high specificity, which approaches 100%. Initially, however, the test was not popular because it required monkey oesophageal tissue as substrate. Since 1994, however, human umbilical cord has been used as substrate and has proved to be even more sensitive and specific than using monkey oesophagus. EMA are not found in healthy individuals, unlike AGA, although false positives have been reported in children with associated gastrointestinal problems. False negatives do occur, especially in children, and where the mucosal lesion is less severe (Kumar *et al*. 1989; Lerner *et al*. 1994; Valdimarsson *et al*. 1996). Dieterich *et al*. (1997) have identified tTG as the auto-antigen with which EMA reacts. The subsequent development of an accurate and inexpensive ELISA for tTG, together with its high sensitivity and specificity, has led to a move towards using tTG as the serological test of choice for the diagnosis of CD (Bazzigaluppi *et al*. 1999; Biagi *et al*. 1999; Gillett & Freeman, 2000*a*; Fabiani *et al*. 2004; Reif & Lerner, 2004; PG Hill, JM Forsyth, D Semeraro and GKT Holmes, unpublished results).

Low levels of tTg antibody can occur in biopsy-proven CD. However, low or negative antibody tests in suspected CD should always raise the possibility of selective IgA deficiency, which is found in 2–3% of individuals with CD, and which affects not only tTg IgA antibodies but also EMA and AGA IgA antibodies. In these circumstances it is recommended that IgA levels are measured and then EMA or tTG IgG antibodies are used to screen for CD (Cataldo *et al*. 2000; Korponay-Szabo *et al*. 2003; Lenhardt *et al*. 2004). Hill *et al*. (2004) have suggested that if tTG antibodies are low (<2·9 units/ml) EMA (IgA) should be measured, and if EMA is positive a biopsy should be done; if EMA is negative IgA should be measured. Screening serology may still be negative in the presence of CD and normal IgA levels (Dickey *et al*. 2000*a*; Rostami *et al*. 2000; Sanders *et al*. 2005). This outcome poses a real diagnostic problem. Where clinical suspicion of CD is high, especially in the presence of risk factors such as family history or type 1 diabetes, then biopsy is necessary and remains the ultimate diagnostic test.

Serum tTG IgA antibodies, or other antibody levels, may also be low because the patient is on a gluten-free diet (GFD). Both tTG and EMA decline in the months following instigation of GFD; by 6 months they will be low and by 12 months they will be negative (Dickey *et al*. 2000*b*; Tursi *et al*. 2003; F Moor, JM Forsyth, PG Hill and GKT Holmes, unpublished results). In some patients antibody levels decline within 4 weeks of starting a GFD, so it is important that patients do not start a GFD until the diagnosis of CD has been established beyond doubt (Midhagen *et al*. 2004). It is not known how long it takes for antibody positivity to develop after the introduction of gluten in CD. If an adult patient has already changed diet it is recommended that they need to have ≤10 g gluten (four slices of bread daily) for 6 weeks before blood testing or gut biopsy (Wahab *et al*. 2001). In the case of children gluten is given either as a fixed daily amount of 5 g or as a free intake of gluten-containing products. For children who may already be on a GFD it may be preferable to use a gluten powder rather than introducing normal gluten-containing foods at this stage.

The usual sequence of events in the diagnosis of CD is, therefore, as follows: clinical suspicion based on symptoms, signs, associated disease or screening in asymptomatic individuals→positive serology→intestinal biopsy→response to GFD. Whilst biopsy is currently regarded as the gold standard for diagnosis, the characteristic 'flat' mucosa of CD is not always seen and various grades of severity are described (Marsh, 1992). Other conditions, such as tropical sprue, protein–energy malnutrition or cow's milk allergy in children, can produce

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Table 2. Studies published since 1997 that have used either antibodies to tissue transglutaminase (tTG) or endomysial antibodies (EMA) to determine the prevalence of coeliac disease

Reference	Country	Population	*n*	Test	Biopsy positive	Rate
Maki *et al.* (2003)	Finland	Schoolchildren 7–16 years	3654	EMA, tTG	Twenty-seven of thirty-six	1:99
Tatar *et al.* (2004)	Turkey	Blood donors	2000	tTG	Seven of twelve	1·3%
Not *et al.* (1998)	USA	Blood donors	2000	AGA, EMA	–	1:250
West *et al.* (2003*b*)	UK	Health study, subjects 45–76 years	7550	EMA	–	1·2%
Hovell *et al.* (2001)	Australia	Health study	3011	EMA	Yes	1:251
Castano *et al.* (2003)	Italy	Children 1·5–2·5 years	613	tTG	Yes	1:118
Fasano *et al.* (2003)	USA	Adults	4126	AGA, EMA, tTG	Yes	1:133
Bingley *et al.* (2004)	UK	Children 7·5 years	5470	tTG	Not done	1·0%
Corazza *et al.* (1997)	Italy	Adults 20–87 years	2237	EMA	Yes	0·18%
Lohi *et al.** (unpublished results)	Finland	Stored sera	7217	EMA, tTG	–	1:93
Mustalahti *et al.*† (unpublished results)	Finland	Adults >30 years	6403	tTG	64%	1:49
Jarry (2003)	Northern Ireland	Adults 32–64 years	4656	tTG	27%	1:63
		Children 12–15 years	1975	tTG	–	1:100
	Italy	Adults and children	4814	tTG	–	1:71
		Children 11–14 years	2612	tTG	–	1:80
	Germany	Adults 25–74 years	4633	tTG	63%	1·74
		Adults 25–74 years	4173	tTG	–	1:232
Schweizer *et al.* (2004)	The Netherlands	Adults	1440	Not given	–	0·35%
Lagerqvist *et al.* (2001)	Sweden	Adults 25–74 years	1850	EMA, tTG	Yes	1:168
Csizmadia *et al.* (1999)	The Netherlands	Children	6127	EMA	Yes	1:198
Pratesi *et al.* (2003)	Brazil	Adults and children	4405	EMA	Yes	0·34%
Gandolfi *et al.* (2000)	Brazil	Blood donors	2045	EMA	Yes	1:681
Gomez *et al.* (2001)	Argentina	Adults	2000	EMA	Yes	1:167
Kolho *et al.* (1998)	Finland	Adults	1070	EMA	Yes	1:130
Johnston *et al.* (1997)	Northern Ireland	Adults	1823	EMA, AGA	Some	1:122

AGA, anti-gliadin antibodies.
*S Lohi, K Mustalahti, K Laurila, O Lohi, H Rissanen, A Reunanen and M Maki.
†K Mustalahti, A Reunanen, M Heuer, M-H Metzger, E Fabiani, C Catassi, L Murray, S McMillan, M Caradonna, E Bravi and M Maki.

a similar picture. In practice, a combination of positive serology and a biopsy in keeping with CD are usually required to put the diagnosis beyond doubt and, thus, justify a lifelong change in diet (Abdulkarim & Murray, 2003). The European Society for Paediatric Gastroenterology, Hepatology and Nutrition (Walker-Smith, 1990) has published revised criteria for the diagnosis of CD, with one biopsy replacing the three originally recommended. The North American Society for Paediatric Gastroenterology, Hepatology and Nutrition (Hill *et al.* 2005) has developed a clinical practice guideline for the diagnosis and treatment of CD in children, and recommends that testing of asymptomatic children who belong to at-risk groups begins at 3 years of age, provided that they have been on an adequate gluten-containing diet for at least 1 year before testing. For adults guidelines have been laid out by the British Society of Gastroenterology (2002).

Prevalence

The prevalence of CD is only now emerging, >50 years after the original intestinal biopsies were done. The development of sensitive and specific serology for CD has opened up new horizons in case finding and diagnosis. Table 2 lists the results of twenty studies published since 1997 that have used either tTG or EMA to determine the prevalence of CD. Overall, these studies involved the screening of 87 904 individuals and the prevalence in these individuals is 1:103, or effectively 1%, which makes CD one of the most prevalent inherited disorders. A recent systematic review of CD prevalence, focusing on the USA and Europe, also reports a value of 1%, with a statistical range of probability of 0·5–1·26% (1:200–1:70; Dube *et al.* 2005).

In terms of the reliability of these data, it is almost certain that they are still an underestimate, because in many studies existing CD cases are not included, very young children have been tested when they may not yet have developed antibodies (Norris *et al.* 2005) and diagnostic criteria may be too rigid. However, not all the prevalence data in Table 2 include both serology and biopsy, which are still both needed for a diagnosis. Furthermore, whilst biopsy remains the gold standard test, its interpretation is by no means black and white. Tiny pieces of tissue are obtained at endoscopy, approximately 2–3 mg, and sampling errors can occur. Moreover, as Marsh (1992) has clearly shown, there are extents of gut damage and early changes such as the presence of a

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few intra-epithelial lymphocytes that are not necessarily considered diagnostic.

There may also be true regional differences in prevalence. Data in Table 2 give a prevalence of 1:94 (1·07%) for European countries, 1:157 (0·64%) for the USA, but for the three reports from South America, the rate is 1:281 (0·36%). However, whilst the European data may be quite robust, the numbers are too small as yet for North and South America to allow discussion of regional variations. More data are needed, especially for the sub-continents of China and India. Nevertheless, the strong genetic background of CD and dietary patterns mean regional variations are likely.

Pregnancy and breast-feeding

Untreated, or undiagnosed, CD is associated with a number of unfavourable fertility and pregnancy outcomes (Norgard *et al*. 1999; Martinelli *et al*. 2000; Kotze, 2004; Ciacci *et al*. 2005). About half the women affected show delayed menarche, reduced fertility and an increase in spontaneous abortion rate. In a UK general-practice-based study (Tata *et al*. 2005) it has been found that crude fertility rates are similar for women with or without CD but age-specific rates are lower for younger patients with CD. For example, fertility rate ratios for women with CD: women without CD are 0·40 (95% CI 0·16, 0·99) for age 15–19·9 years and 0·84 (95% CI 0·61, 1·16) for age 20–24·9 years, whilst in older age-groups fertility rates are greater, 1·39 (95% CI 1·06, 1·83) for age 35–39·9 years, indicating that women with CD probably have their babies at a later age, which is consistent with the socio-economic profile of women with CD. The relative risk for miscarriage is ≤8·9 (Ciacci *et al*. 1996) and intrauterine growth retardation occurs, with average birth weights that are ≤800 g lower (Martinelli *et al*. 2000; Ciacci *et al*. 2005). Of the couples who are infertile 3% have CD, and in couples with otherwise unexplained infertility the rate is 8%. Male fertility may be affected (Meloni *et al*. 1999). Adherence to a GFD, however, reduces these risks to the same as that in the rest of the population (Ciacci *et al*. 1996; Norgard *et al*. 1999; Martinelli *et al*. 2000), but may not affect fertility rates (Tata *et al*. 2005). Moreover, the risks to baby and mother may be less in those individuals who have only minor symptoms of CD and are diagnosed by screening blood test, although the risk of anaemia and spontaneous abortion remains (Greco *et al*. 2004).

The advice on nutrition (Department of Health, 1996) and alcohol intake (Department of Health, 1995; Royal College of Obstetricians and Gynaecologists, 1999) given to women with CD who become pregnant whilst adhering to a GFD should be similar to the general dietary guidance given during pregnancy, including preconceptual supplementary folic acid (400 µg/d), which should be continued throughout the first trimester of pregnancy (Department of Health, 2000). There are no specific recommendations on Ca intake during pregnancy, but the advice should be tailored to the individual. Supplementation needs to be considered on an individual basis, with particular reference to Fe, Ca, folic acid and vitamin B_{12} status.

Once the baby is born the question arises as to when to introduce gluten-containing foods. The UK Department of Health (1994) and Food Standards Agency (2002), the World Health Organization (Kramer & Kakuma, 2002) and the American Academy of Pediatrics (Hill *et al*. 2005) recommend breast milk alone for the first 6 months and no wheat-based foods. In Sweden Ivarsson *et al*. (2000, 2002) have studied a large group (627) of subjects with CD and controls (1254) and have related CD to infant feeding patterns. They suggest that the risk of CD is reduced (OR 0·59 (95% CI 0·42, 0·83)) if breast-feeding is continued when gluten-containing foods are introduced, and they recommend that these foods are introduced gradually. In Sweden gluten-free foods are allowed at between 4 and 6 months (van Odijk *et al*. 2004), although half the mothers delay introducing them until 6 months. In the UK the British Dietetic Association's Paediatric Group Position Statement on Breastfeeding on to Solid Foods (British Dietetic Association, 2005) states that 4 months or 17 weeks should be regarded as the earliest age at which solids should be introduced and that gluten-containing foods should not be introduced until after 6 months.

In a prospective study of 1560 children in the USA at increased risk of CD (having either HLA-DR3 or DR4 alleles) exposure to wheat, barley or rye in the first 3 months of life has been shown to increase the risk of CD fivefold compared with those who are not exposed until 4–6 months (Norris *et al*. 2005). Interestingly, in this study, in which children had tTG antibody levels measured regularly from age 9 months, the mean age at which the first positive test was recorded was found to be 4·7 (SD 1·5) years. Studies in other countries, although perhaps not as comprehensive, have not found a relationship between the timing of the introduction of gluten-containing foods and risk of CD (Cataldo *et al*. 1995; Ascher *et al*. 1997; Peters *et al*. 2001). However, Peters *et al*. (2001) have shown a substantial lowering of risk for developing CD in children breast-fed for >2 months as compared with those breast-fed for <2 months, including partial breast-feeding. Introduction of wheat before 6 months is more likely to lead to failure to thrive, whilst breast-fed children who develop CD are often diagnosed late and have milder and more atypical symptoms (D'Amico *et al*. 2003).

This area is a very important for further prospective studies. If the risk of CD can be reduced by continuous breast-feeding and avoidance of gluten, then prevention of CD becomes possible and a lot of questions about its cause are raised. Meanwhile, gluten should not be introduced before 6 months and any weaning foods before this time should be gluten-free. This advice is particularly important for families in which there is a history of CD. Breast milk is protective and can delay the onset of symptoms in predisposed infants.

Risk of malignancy

There is undoubtedly an increased risk of malignancy in CD, but this risk is probably confined to two quite rare types of cancer (Table 3) and diminishes with time from diagnosis and with good dietary compliance. Almost as

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Table 3. Risk of cancer in coeliac disease

Increased	Decreased
Definite	
Non-Hodgkins lymphoma	Breast
Small bowel adenocarcinoma	
Possible	
Oesophagus	Lung
Melanoma	
Large bowel	
Liver	
Oropharyngeal	
Pancreas	
No change	
Stomach	
Prostate	
Ovary	
Brain	

Table 4. Conditions more common in coeliac disease

Diabetes (type 1)
Thyroid disorders (autoimmune or Graves)
Sjogren's syndrome
Adrenocortical failure (Addisons)
Liver disease (raised transaminases and primary biliary cirrhosis)
IgA deficiency
Lymphocytic or microscopic colitis
Down's syndrome
Unusual neurological disorders
Dental enamel defects
Turner syndrome

soon as CD had been defined and small bowel biopsy became popular, there was shown to be an increased risk of lymphoma of the small bowel (Gough *et al*. 1962). Reports then followed on increased risk of gastrointestinal malignancy such as orophoryngeal and oesophageal cancer (Holmes *et al*. 1989; Logan *et al*. 1989) and, more recently, other cancer risks have been identified in some but not all studies, e.g. melanoma, liver and pancreatic cancer (Askling *et al*. 2002; Green *et al*. 2003). Risk of adenocarcinoma of the small bowel has been found to be consistently increased (Askling *et al*. 2002; Howdle *et al*. 2003; Peters *et al*. 2003; Rampertab *et al*. 2003).

The principal cancer that is increased in CD is lymphoma, of which non-Hodgkins lymphoma is the principal type. Both B- and T-cell non-Hodgkins lymphomas occur, with the T-cell type probably being the more common (Catassi *et al*. 2002; Green *et al*. 2003; Smedby *et al*. 2005), depending on the population being studied. However, it should be remembered that whilst the risk of non-Hodgkins lymphoma may be increased by between 3-fold and 9-fold, the overall risk to the population is <1% and so this type of cancer remains uncommon even in CD. Similarly, adenocarcinoma of the small bowel, although ten to thirty-four times more common in CD (Askling *et al*. 2002; Peters *et al*. 2003; Green *et al*. 2003), nevertheless remains a very rare tumour.

On a more positive note, the risk of some of the very common cancers appears to be reduced in CD, particularly breast cancer, for which the risk is reduced to about one-third (Askling *et al*. 2002; Card *et al*. 2004; West *et al*. 2004*b*), and lung cancer, which is reduced in some studies (West *et al*. 2004*b*). However, the Nottingham group, who have reported observations in this area of CD and malignancy since 1989, have noted that fewer patients with CD are smokers (Austin *et al*. 2002). The mechanism that leads to these reduced risks needs further research.

Equally encouraging is the observation that risk of malignancy, except possibly non-Hodgkins lymphoma, diminishes with time after diagnosis of CD and by 15 years the overall risks are no different from those for the general population (Askling *et al*. 2002; West *et al*. 2004*b*). CD diagnosed in childhood carries no additional risk of malignancy. Most importantly, the risk diminishes only in those compliant with a GFD (Holmes *et al*. 1989; Logan *et al*. 1989; Corrao *et al*. 2001), although Ciacci *et al*. (2005) have reported that diagnosis in childhood and gluten withdrawal is protective even if individuals subsequently become re-exposed to gluten.

Cancer risks are probably not increased in DH (Askling *et al*. 2002) unless patients fail to adhere to a GFD, in which case the risk of lymphoma is increased (Hervonen *et al*. 2005).

Overall, there is clearly increased risk for two types of cancer, lymphoma and adenocarcinoma of the small bowel. However, the risk of breast cancer is reduced and possibly also the risk of lung cancer. Moreover, the risk appears to diminish following diagnosis and is the same as that for the general population after 15 years on a GFD. CD diagnosed in childhood carries no extra risk of malignancy, neither does DH. However, the fundamental precondition is that a strict GFD is followed.

Associated conditions

A number of diseases seem to occur more commonly in CD (Collin *et al*. 1994; Feighery, 1999; Table 4). Of these conditions, type 1 diabetes is probably the most important, occurring in about 5% of patients with CD, and when patients with type 1 diabetes are screened for CD 6–10% are antibody and/or biopsy positive (Gillett *et al*. 2001; Hansen *et al*. 2001; Not *et al*. 2001; Valerio *et al*. 2002; Arato *et al*. 2003; Ashabani *et al*. 2003). Moreover, the siblings of children with diabetes, who do not have diabetes themselves, show an increased frequency of CD of 1·9–3·8% (Not *et al*. 2001; Sumnik *et al*. 2005) and the risk of type 1 diabetes is also increased in individuals with DH (2·3%) and their relatives (3%; Hervonen *et al*. 2004). A common genetic predisposition has been suggested, with HLA-DQB1*02 or *0302 present in all patients with both conditions (Martin-Villa *et al*. 2001; Saukkonen *et al*. 2001). Patients with diabetes who have CD show signs of poor nutrition (Hansen *et al*. 2001) and improve with a GFD, with which they show good compliance (Not *et al*. 2001; Saadah *et al*. 2004). Thus, screening of all patients with type 1 diabetes and probably their first-degree relatives is desirable.

Approximately 5% of the patients with CD have thyroid disorders (either autoimmune (Hashimoto's) or Graves

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disease), about twice the prevalence in the general population (Collin *et al*. 1994; Ciacci *et al*. 2005). Again, it is worth screening patients with these disorders for CD, because the prevalence of CD in Graves disease is about 4·5% (Ch'ng *et al*. 2005) and patients with Hashimoto's disease who are sero negative for CD show increases in the number of γ δ T-cell receptors bearing I-E lymphocytes and increases in mucosal T-cell activation (Valentino *et al*. 2002), which could be construed as early or subclinical CD.

Other autoimmune disorders seen in CD include Sjogren's syndrome (a chronic inflammatory disorder of probable autoimmune nature characterised by infiltration of the exocrine glands, particularly the salivary and lacrimal (tear) glands, by lymphocytes and plasma cells), about 3% of patients with CD (Collin *et al*. 1994), and when patients with Sjogren's syndrome are screened for CD 4·5% are biopsy positive for CD (Szodoray *et al*. 2004). In patients with adrenocortical failure, of whom 7–12% are reported to have CD (O'Leary *et al*. 2002; Myhre *et al*. 2003), screening for CD again seems worthwhile.

Untreated CD is frequently associated with silent liver disease, i.e. elevated levels of transaminases. A recent systematic review of this condition by Duggan & Duggan (2005) has identified six studies that include liver biochemistry, indicating that 42% of the patients newly-diagnosed with CD have raised transaminases. Treatment with a GFD leads to the majority of biochemical and early histological abnormalities reverting to normal. Conversely, 3–4% of the patients with non-alcoholic steatohepatitis have biopsy-positive CD (Bardella *et al*. 2004). In 10% of Italian patients with biliary cirrhosis there is an increased risk of CD (Floreani *et al*. 2002), but no risk of CD is apparent in Poles (Habior *et al*. 2003). Cholestatic liver disease has also been reported (Lawson *et al*. 2005).

Finally, there are a number of other associated disorders such as Down's syndrome (Morris *et al*. 2000; Goldacre *et al*. 2004), unusual neurological conditions (Feighery, 1999), lymphocytic and microscopic colitis (Gillett & Freeman, 2000*b*; Olesen *et al*. 2004), dental enamel defects (Ciacci *et al*. 2005), depression (Addolorato *et al*. 2001; Ciacci *et al*. 2005) and Turner syndrome (a rare chromosomal disorder (usually XX) of females characterised by short stature and lack of sexual development at puberty; Gillett *et al*. 2000).

There is no rational explanation for this disparate collection of disorders, but it is clearly worth screening patients with type 1 diabetes, thyroid disease, adrenocortical failure, Sjogren's syndrome, unexplained raised levels of liver transaminases and microscopic colitis for CD.

Bones

One of the earliest observations, in the 1930s, in patients with CD presenting with classic malabsorptive symptoms was the association with bone disease, particularly osteomalacia (Bennet *et al*. 1932). What was not apparent at the time was the higher prevalence of less-severe bone disease in CD, which has only become apparent with the advent of dual-energy X-ray absorptiometry in the late 1980s (Caraceni *et al*. 1988). Since then, there have been a number of reports showing clear evidence of reduced bone mineral density (BMD), osteopenia or osteoporosis in 20–50% of the patients newly diagnosed with CD (Butcher *et al*. 1992; Corazza *et al*. 1995, 1996; McFarlane *et al*. 1995; Kemppainen *et al*. 1999*a*; Cellier *et al*. 2000; Meyer *et al*. 2001). 'Thin' bones are, therefore, the commonest complication of CD.

The cause of this disorder is likely to be chronic malabsorption of Ca, leading to secondary hyperparathyroidism and increased bone turnover. Contributing factors may be reduced physical activity, low Ca intakes and low BMI. Increases in markers of bone turnover, formation and resorption, such as bone-specific alkaline phosphatase, urinary hydroxyproline, serum osteocalcin and procollagen I carboxyterminal propeptide, are seen in untreated CD (Corazza *et al*. 1995; Sategna-Guidetti *et al*. 2000), along with increased levels of intact serum parathyroid hormone and serum 1,25-dihydroxycholecalciferol. Similar changes in bone are also seen in Crohn's disease, but what is surprising about the finding in CD is the occurrence of osteopenia or osteoporosis even in patients with very minor presenting symptoms.

The consequences of these bone changes are probably an increase in aches and pains but possibly not much risk of fracture. Increased fracture is reported in a number of big studies of CD, but the risk is small. In 4732 patients with CD in the UK the hazard ratio for hip fracture was found to be 1·90 (95% CI 1·20, 3·02), and for fracture of the ulna or radius 1·77 (95% CI 1·35, 2·34; West *et al*. 2003*a*). Higher risks have been reported (Vazquez *et al*. 2000), which interestingly may relate to the severity of presenting symptoms. Moreno *et al*. (2004), in 148 patients newly-diagnosed with CD, have shown that in the patients who presented with chronic diarrhoea, overt malabsorption, weight loss and malnutrition the fracture risk in the peripheral skeleton is increased compared with age- and gender-matched controls (odds ratio 5·2 (95% CI 2·8, 9·8)), while in those patients who presented subclinically with anaemia or osteopenia or just on screening the fracture risk is not increased compare with the controls (odds ratio 1·7 (95% CI 0·7, 4·4)). In some studies no increase in fracture risk has been observed (Vestergaard & Mosekilde, 2002; Thomason *et al*. 2003), probably because large numbers of patients need to be studied to detect small changes in risk.

BMD does improve with a GFD but may not return to that seen in a matched population (Corazza *et al*. 1995; McFarlane *et al*. 1995; Sategna-Guidetti *et al*. 2000; Pazianas *et al*. 2005). A study that followed patients with CD on a GFD for 5 years (Kemppainen *et al*. 1999*b*) has shown that BMD is increased by 2% in the lumbar spine, 1% at the femoral neck and 6% at the femoral trochanter, with most of this increase occurring in the first year of treatment. Any halt to the progressive decline in BMD seen in older women particularly is important. Patients who start off with secondary hyperparathyroidism seem to do less well after 3 years on a GFD (Valdimarsson *et al*. 2000).

Management of low BMD and CD, apart from a GFD, should follow conventional lines, including increasing

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Table 5. Nutritional indices in subjects with coeliac disease

At presentation:
Reduced BMI
Low serum Ca
Reduced Hb
Reduced serum or erythrocyte ferritin
Reduced serum albumin
Low plasma cholesterol
Low serum folic acid
Raised plasma homocysteine
Long-term problems:
Ca and bones
Folate
Fe

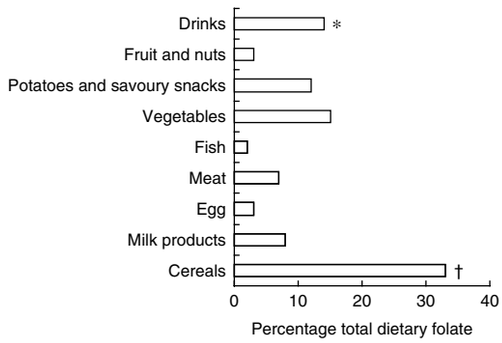

Fig. 1. Sources of dietary folate. * Beer 8%. † Breakfast cereals 15%. (From Henderson *et al.* 2003.)

exercise, stopping smoking, avoiding alcohol excess and ensuring an adequate Ca intake of ≥1·5 g/d in adults (the recommended Ca intake for adults with CD is 1·5 g/d; Scott *et al.* 2000) using supplements if necessary. Dairy products such as milk, cheese and yoghurt should be incorporated to provide prime sources of Ca (Scott *et al.* 2000). Hormone-replacement therapy is useful in post-menopausal women, and in persistent osteopenia biophosphonates are of proven benefit (Scott *et al.* 2000). Reduced BMD is also seen in DH, although to a lesser extent than in CD, except where BMI is <20 kg/m^2 (Di Stefano *et al.* 1999).

Potential nutritional problems

At presentation, or on diagnosis, subjects with CD show clear differences in nutritional status from non-CD controls (Kemppainen *et al.* 1998; Sategna-Guidetti *et al.* 2000; Tursi *et al.* 2001; Gillett *et al.* 2003; Ciacci *et al.* 2005; W Dickey, M Ward, M Traynor, C Hackett, G Horigan, S Patton, M O'Kane and H McNulty, unpublished results). Table 5 lists the most consistently found differences, which include body weight (BMI reported in the range 18–20 kg/m^2), lower Hb (1·2 g/l compared with 1·3 g/l in controls) and low ferritin and Fe, albumin, Ca, cholesterol and folate, associated with raised plasma homocysteine. These differences do not qualify as deficiencies and not all newly-diagnosed patients with CD show them. Nevertheless, they improve with a GFD (Sategna-Guidetti *et al.* 2000) and are less marked in partly-treated patients (Ciacci *et al.* 2005). They are consistent with generalised malabsorption associated with a defect in transport in the duodenum and jejunum. Occasional reports of vitamin B_{12} deficiency (see Kemppainen *et al.* 1998) are less easy to understand.

Surprisingly, there are very few papers on any long-term problems associated with nutrition in CD, apart from the well-recognised complication of osteoporosis to which a number of factors may contribute (see earlier discussion, p. 440). At presentation patients with CD have a lower BMI than matched controls, which seems to continue in the long term. At three-yearly follow-up a group of seventy-one adult patients with CD seen in an Italian clinic, who were on a strict GFD and asymptomatic, underwent nutritional and dietary assessment (Bardella *et al.* 2000). BMI (kg/m^2) was found to be significantly lower than in a control population in both men (21·9 (SD 2·9) for men with CD *v.* 23·5 (SD 2·9) for the controls; $P>0·05$) and women (20·9 (SD 2·7) for women with CD *v.* 22·4 (SD 4·3) for controls; $P<0·03$), and energy intakes were found to be lower by 1000–1500 kJ. Body fat and lean body mass were also found to be lower in patients with CD.

However, most patients with CD seem to put on weight after starting a GFD (Hallert *et al.* 2002), and the reported lower BMI may be related to the fact that patients with CD are more health-conscious than the increasingly-obese general population rather than to a GFD leading to inadequate energy intake (GG Robins, S Hamlin and PD Howdle, unpublished results).

More importantly, however, there may be long-term problems with folate status. In a study of thirty adults with CD in biopsy-proven remission for 8–12 years on a GFD (Hallert *et al.* 2002) low plasma folate levels were found in 20% of the subjects and low pyridoxal 5′-phosphate levels in 37% of the subjects. Mean daily folate intake was also significantly lower for patients with CD (184 µg/d) than for the controls (206 µg/d; $P<0·05$). Plasma homocysteine concentrations were found to be significantly higher for male patients with CD (13·6 µmol/l) than for controls (11·2 µmol/l; $P<0·05$) and were also higher, but not significantly, in female patients with CD.

Clearly, more studies that look at vitamin and mineral status in CD in the long term are needed; with raised plasma homocysteine now linked to increased risk of CVD (Kerins *et al.* 2001) and low folate intakes linked to colo-rectal cancer (Mason, 2002) these findings could be important. They are also relevant because 33% of the dietary folate comes from cereals and a further 8% from beer, both restricted food groups for individuals with CD (Fig. 1).

The importance of chronic problems with nutrition is unclear, apart from those related to bone disease. However, a disturbing preliminary report from Finland (Verkasalo *et al.* 2003) has indicated that twenty-one of 2427 Finnish adults attending a cardiovascular risk clinic were found to be antibody positive for tTg and EMA, but were not known to have CD. Fewer of the antibody-positive group had a university degree (5·3% for those who were antibody

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positive *v*. 15·6% for the rest) or were in 'executive or expert positions in (their) working life' (28% for those who were antibody positive *v*. 45% for the controls). The authors have suggested that subjects with 'silent' CD might have concentration difficulties at school. A study of adolescents with newly-diagnosed CD (Pynnonen *et al*. 2005) has shown that pre-GFD those subjects with depression had lower blood tryptophan:competing amino acid values and free tryptophan concentrations compared with those subjects without depression. The improvements in serum competing amino acid levels and in behaviour after 3 months on a GFD give support to previous findings in patients with CD that they show symptoms of depression and disruptive behaviour, in theory related to serotonergic dysfunction, in general preceding diagnosis and treatment with the GFD (Pynnonen *et al*. 2004). Furthermore, these improvements suggest that serotonergic dysfunction related to impaired availability of tryptophan may play a role in vulnerability to depressive or behavioural problems in untreated CD.

On a more positive note, death from CVD is thought to be reduced in CD (Whorwell *et al*. 2004) and risk factors for CVD are reduced in undiagnosed (sero-positive) subjects compared with controls chosen from the General Practice research database, which is a longitudinal primarycare database for more than eight million registered individuals (West *et al*. 2003*b*). These factors include lower blood cholesterol, lower LDL-cholesterol, lower BMI, lower blood pressure and fewer smokers. In established CD rates of myocardial infarction and stroke do not seem to be markedly different (West *et al*. 2004*a*); nevertheless, blood pressure is lower, as is blood cholesterol.

Dietary management

Treatment for CD requires elimination of the gluten found in wheat, barley and rye from the diet (Anderson *et al*. 2000). Studies in recent years indicate that avenins from oats are not toxic for patients with CD, either for adults (Janatuinen *et al*. 2002) or children (Hogberg *et al*. 2004), but recommendations on the inclusion of oats in the GFD vary in practice. One major issue in relation to the safety of oat products is contamination with gluten-containing cereals (Thompson, 2005). In addition, some patients with CD are sensitive to uncontaminated oats, so individual advice on suitability and safe amounts needs to be based on monitoring and review of progress (Lundin *et al*. 2003). The GFD can be restrictive in terms of elimination of staple foods such as bread, pasta and breakfast cereals, and replacement with gluten-free alternatives. There is limited information available about the composition of specialist gluten-free products. However, there is evidence from the USA that they may be lower in fibre, Fe, folate, thiamin, riboflavin and niacin (Thompson, 1999, 2000, 2005). Management of a GFD is based on using gluten-free cereals such as rice, millet (*Panicum milaiceum*), maize and buckwheat (*Fagopyrum esculentum* Moench.) and also including a variety of other grains, seeds and starchy sources, including amaranth (*Amaranthus caudatus* L.), teff (*Eragrostis tef*), quinoa (*Chenopodium quinoa* Willd.), soyabean, potato and plantains (*Musa paradisiaca* L.; Table 6).

Table 6. Checklist of gluten-free foods

Amaranth (*Amaranthus caudatus* L.)
Buckwheat (*Fagopyrum esculentum* Moench.)
Maize
Millet (*Panicum milaiceum*)
Nuts
Potato
Quinoa (*Chenopodium quinoa* Willd.)
Rice
Sorghum
Soyabean
Tapioca*
Teff (*Eragrostis tef*)

*Starch derived from the cassava (*Manihot esculenta*) root.

Dietary compliance

Dietary compliance is key in the successful treatment of CD (Case, 2005). There is evidence to suggest that adherence to the GFD of patients diagnosed with CD depends on the severity of symptoms; the more symptomatic the patient the greater the adherence to the GFD (Westman *et al*. 1999). Numerous studies indicate that adult dietary compliance tends to be varied (17–45%; Kluge *et al*. 1982; Mayer *et al*. 1991; Bardella *et al*. 1994; Vahedi *et al*. 2003). There is an indication that dietary compliance is better when the CD is diagnosed in early childhood (Fabiani *et al*. 2000; Hogberg *et al*. 2004).

Dietary compliance can be assessed by diet history or measurement of serum antibodies (Burgin-Wolff *et al*. 2002, Ciacci *et al*. 2002). Non-compliance may occur for a number of different reasons, including poor perception of the quality and availability of gluten-free food products compared with gluten-containing comparisons, lack of support, dietary education and information, and poor understanding of food labels (Pietzak, 2005).

Common reasons for persisting symptoms are lactose intolerance, pancreatic insufficiency and microscopic colitis. However, persistent symptoms are usually the result of inadvertent ingestion of gluten (Ahmad *et al*. 2002), which contaminates many products in the food chain (Ciacci & Mazzacca, 1998; Collin *et al*. 2004; Thompson, 2005).

Referral to a state-registered dietitian

Referral to a state-registered dietitian is essential in order to adopt a problem-solving approach with on-going review and support in the management of CD and any associated conditions or secondary problems (Anderson, 2005). Dietetic intervention needs to be based on individual assessment of nutritional requirements, but is also dependent on socio-economic and cultural factors (Bardella *et al*. 1994). The British Society of Gastroenterology (2002) guidelines on the management of CD recommend that patients should be seen by a dietitian

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at diagnosis and then at regular intervals in order to provide dietary education and assess nutritional status. In patients with a satisfactory response to the GFD there should be a minimum of six-monthly dietetic review. On-going support by the healthcare team, including the general practitioner, gastroenterologist, dietitian, pharmacist and practice nurse, is essential. Children require specific monitoring of growth and development and nutritional requirements, and a paediatric gastroenterologist and paediatric dietitian should be involved.

Dietary intervention needs to take into account increased requirements for Ca and advice to promote good bone health. Achieving the recommended intake of Ca for adults of 1·5 g/d (Scott *et al*. 2000) in patients with CD with low bone density or osteoporosis requires assessment, support and on-going advice. Long-term maintenance of the GFD is pivotal in optimising absorption.

Although other dietary deficiencies, including Fe deficiency resulting in anaemia, may resolve over a period of time once the patient follows a GFD, it seems reasonable to ensure rapid correction with appropriate supplements. Patients need individual advice on appropriate supplementation in the management of CD (British Society of Gastroenterology, 2002).

Individuals with CD may also require dietetic intervention for weight management, management of cardiovascular risk factors and other possible concomitant conditions. Patients may also have additional dietary considerations such as lactose intolerance, diabetes and hypercholesterolaemia. Solving individual problems requires on-going review and monitoring, and needs to be based on medical and dietary history.

Trouble-shooting and consideration of the elimination of ingredients that contain a low level of gluten within the Codex standard (Codex Alimentarius Commission, 1981, 1983), including Codex wheat starch, malt extract (used particularly in breakfast cereals) and oats, may be necessary in the dietetic management of patients with CD. An individualised approach is essential.

Although management of patients with CD in the UK is not always consistent with the British Society of Gastroenterology (2002) recommendations for regular review, dietitian-led coeliac clinics are evolving as a way forward, using healthcare resources most effectively and improving care of patients with CD (Wylie *et al*. 2005).

Gluten-free standard

On-going problems may also arise because individuals do not maintain a low-enough gluten intake. This situation arises because foods can be labelled ‘gluten-free’ as long as they have a level of gluten <200 mg/kg, the internationally-accepted Codex standard that is applied in many parts of Europe, including the UK (Codex Alimentarius Commission, 2004*a*,*b*). In practice, the Codex standard was developed in line with the introduction of gluten-free breads and flour mixes containing Codex wheat starch. These products have improved quality and compliance on the GFD (Collin *et al*. 2004). A Finnish group have reported a safe and practical threshold of 100 µg gluten/g, providing that the total daily intake does not exceed 300 g wheat-starch-based gluten-free flour (Collin *et al*. 2004).

The Codex standard also relates to a method of detection of gluten in foods (Food and Agriculture Organization/World Health Organization, 2003). Further work is being carried out to refine the methodology to assess the gluten content of foods (Valdes *et al*. 2003). There is a global debate about the gluten standard as the Codex Committee on Nutrition and Foods for Special Dietary Uses awaits further scientific evidence to support a threshold or tolerance level. Studies indicate that Codex wheat-starch products are safe for the majority of patients with CD (Ciclitira *et al*. 1984, 1985; Kaukinen *et al*. 1999), but there have been studies that indicate that some individuals continue to have symptoms on these products (Biagi *et al*. 2004), which resolve when the products are discontinued (Chartrand *et al*. 1997; Faulkner-Hogg *et al*. 1999; Peraaho *et al*. 2003). One of the issues relating to the Codex standard and the inclusion of Codex wheat-starch products, or other products such as malted breakfast cereals or oats, that may contain low levels of gluten is recognition that there is an additive effect of eating a low level of gluten and there are considerable differences between individuals with CD in their response to gluten ingestion (Ciclitira *et al*. 2005).

Food labelling

Education on the GFD requires continuing information on food labelling in order for patients with CD to understand food labels and be able to identify gluten-free foods. Dietary education needs to take into account developments in food labelling. A new EU labelling Directive 2003/89/EC (European Commission, 2003), which provides guidelines for the food industry on labelling of allergens in food products was published on 25 November 2003 and will be obligatory by 25 November 2005. This new guidance will help patients with CD to identify gluten in food products. All ingredients will be listed and any allergen present highlighted as ‘contains gluten’ or ‘contains wheat’ (European Commission, 2000).

Gluten-free foods

There are different ranges of specialist gluten-free foods, e.g. bread and pasta, to replace standard wheat-containing varieties. Some of these foods can be obtained on prescription, from health-food shops, mail order, pharmacies, the internet and supermarkets, with some big retailers producing their own ranges of gluten-free foods. The availability of gluten-free foods on prescription can aid compliance with the GFD (Collin *et al*. 2004).

Gluten-free foods on prescription

Gluten-free foods available on prescription tend to be staples such as bread, flour, bread and cake mixes, pizzas, crackers and pasta. Patients may need to obtain samples of products from manufacturers in order to understand exactly which products they require on prescription on a regular

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basis. The local dietitian can provide specific guidance on products and manufacturers.

The gluten-free foods that are available on prescription are listed in the National Health Service Drug Tariff for England and Wales, which is compiled on behalf of the Department of Health by the Prescription Pricing Authority (Drug Tariff, Part XV; Prescription Pricing Authority, 2005) and agreed by the Advisory Committee on Borderline Substances. Patients with CD still have to pay for prescriptions, unless they meet the criteria for exemption, i.e. children, full-time education, the elderly or those individuals on income support or other benefits.

There are new guidelines available to healthcare professionals on reasonable quantities of gluten-free foods for individual patients, based on nutritional requirements (Good Relations Healthcare, 2004). Gluten-free food products have been allocated unit values and there are suggestions relating to the number of units that should be allocated on a regular monthly basis to individuals based on age and gender.

Coeliac UK's Food and Drink Directory

Coeliac UK (High Wycombe, Bucks., UK) produces a range of resources that provide information on CD and the GFD. Processed foods are limited as they may contain added thickeners, flavourings and anti-caking agents, which may be derived from wheat. One such resource is the Food and Drink Directory (Coeliac UK, 2005*a*), which is updated on a monthly basis (Coeliac UK, 2005*b*) and lists >11 000 foods that are gluten-free, including baby foods, foods available on prescription, bulk-catering products and processed foods.

Conclusion

CD, one of the commonest inherited disorders, can manifest itself in many ways and at all ages. Although an autoimmune condition, it is unique in being entirely curable by diet. However, complete avoidance of gluten is a real challenge for individuals with CD, as 'gluten-free' cereal products are allowed to contain ≤200 μg gluten/g, and there is evidence of widespread contamination of many naturally gluten-free foods with wheat. In addition, current market trends show that consumers are eating more processed foods, in which wheat is commonly used as an ingredient. Clear labelling, education and awareness are key issues.

Important questions about CD remain unanswered, including the nature of the genetic abnormality, the precise mechanism of damage to the gut mucosa, the reasons for so many systems of the body to be involved, the association with other conditions such as type 1 diabetes and tolerance levels of gluten in individuals. Further evidence is awaited that will provide a more accurate picture of the impact of low levels of gluten ingestion and facilitate a more definitive line on the gluten standard as defined by the Codex Alimentarius Commission (2004*a*,*b*). CD is now firmly on the agenda, 50 years after the first gut biopsies were done.

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