# Coeliac disease

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## Abstract

Coeliac disease (CD) is a common, chronic, immune-mediated small bowel enteropathy resulting from gluten exposure in genetically susceptible individuals. Considerable clinical and immunopathological heterogeneity is seen in newly diagnosed patients, and the diagnosis is not always straightforward even for experienced physicians. Population screening using tissue transglutaminase 2 has revealed a higher prevalence of seropositivity than previously appreciated. There is a wide differential diagnosis for mucosal villous atrophy, crypt hyperplasia and increased intraepithelial lymphocyte concentrations. Life-long adherence to a gluten-free diet is currently the only recommended treatment for CD, although many newer approaches are being explored. CD is rightly described as a multisystem disorder and is associated with other gastrointestinal and non-gastrointestinal related disorders, numerous complications and possibly reduced survival. The landscape has recently expanded with the identification that some patients with symptoms suggestive of CD but without the mucosal changes seem to respond to a gluten-free diet. This group of patients are currently labelled as having non-coeliac gluten sensitivity. Controversy exists over whether this is a separate disease entity. This review briefly discusses the important clinical, immunological and therapeutic aspects of CD.

**Keywords** Coeliac disease; gluten-free diet; immunopathology; MRCP; non-coeliac gluten sensitivity; tissue glutaminase 2 (tTG2)

## Key points

- Coeliac disease is a chronic, immune-mediated gluten-sensitive enteropathy requiring a life-long gluten-free diet
- The prevalence of coeliac disease is high in developed countries, and it is important to screen for the condition in high-risk population groups
- There are numerous causes of subtotal villous atrophy, including drugs, that must be considered before making a diagnosis of coeliac disease
- Future therapeutic strategies may include drugs targeted to inhibit the toxic potential of gluten, antibodies to inhibit the cytokine interleukin 15, or inhibitors of tissue transglutaminase 2

## Introduction

Samuel Gee first described the classical presentation of coeliac disease (CD), which he termed the 'coeliac affection', in a lecture at the Hospital for Sick Children, Great Ormond Street in 1887,[1] subsequently published in the St Bartholomew's Hospital Reports of 1888. Progress in understanding CD was, however, hampered by an inability to recognize the autoantigen responsible for the immune activation causing the small bowel damage and malabsorption.

It was not until the 1940s that the Dutch paediatrician Dr Willem Karel Dicke and his colleagues identified that wheat ingestion was responsible for initiating the immunopathology resulting in malabsorption. Dicke noticed that a shortage of bread, widespread throughout Europe in the early 1940s because of World War II, led to a significant fall in the mortality rate among children affected by CD, from >35% to essentially zero. The mortality increased again when wheat was available in the post-war period.

Considerable advances in our understanding of CD have occurred since then, not least immunological advances that have elucidated the underlying mechanisms leading to villous atrophy. More than 95% of patients with CD carry human leukocyte antigen (HLA)-DQ2 or HLA-DQ8 heterodimer, which plays a pivotal role in the body's response to deamidated gluten peptides.

The only treatment for CD is a life-long adherence to a gluten-free diet (GFD). Population screening has revealed a higher seroprevalence of tissue transglutaminase 2 (tTG2) than previously suspected, with an estimated prevalence of 1% in Western countries and a higher prevalence in individuals from Northern European countries. Considerable heterogeneity exists among studies estimating CD prevalence rates in different countries, but rates of antibody seropositivity are often greater than sometimes appreciated.[2] This has given rise to the concept of the 'coeliac iceberg' (Figure 1) — individuals with overt clinical symptoms of malabsorption and weight loss constitute the tip of the iceberg, with the remainder made up of silent, potential and latent disease.

## Aetiology

CD is known to result from dietary exposure to gluten in genetically predisposed individuals. The hallmark of the pathogenesis is an adaptive immune response controlled by gluten-specific CD4+ cells that recognize deamidated gliadin peptides presented by the disease-associated HLA-DQ2 and HLA-DQ8 molecules. Activated CD4+ cells release cytokines including interferon-$\gamma$ and tumour necrosis factor (TNF)-$\alpha$ along with activation of matrix metalloproteinases (MMPs), which are responsible for the tissue damage. B cells are also stimulated to produce antibodies to tTG2 and gluten. A simplified schematic is outlined in Figure 2.

Exclusion of gluten from the diet reduces antibody production, and the concentration of tTG2 can therefore be used in monitoring dietary compliance.

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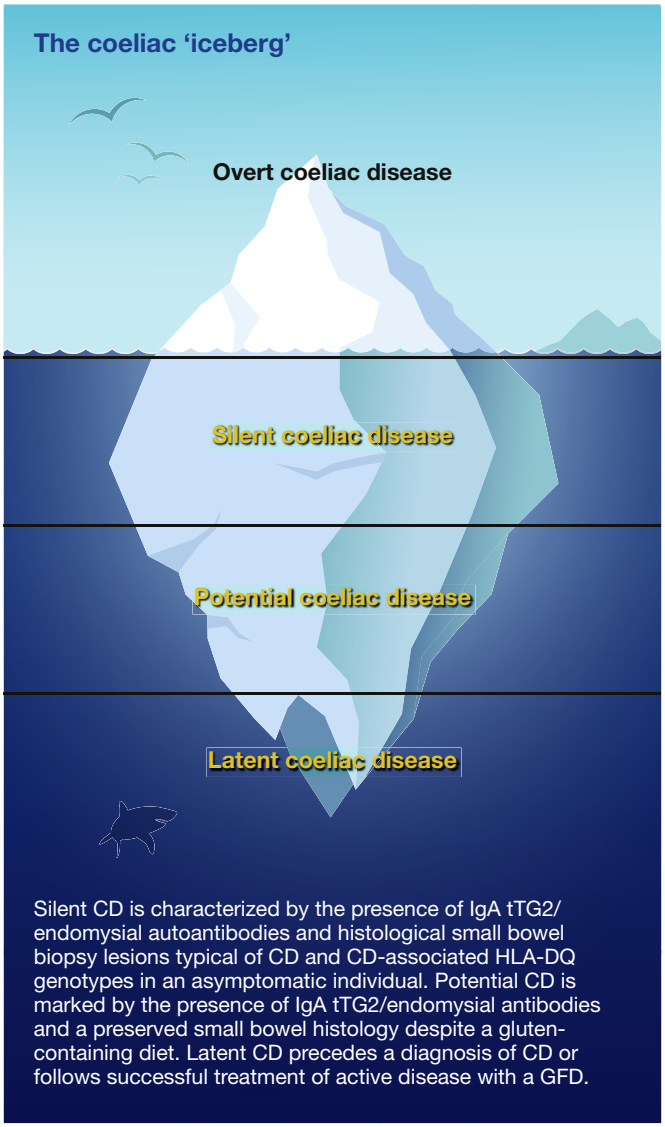



**Figure 1**

## Diagnosis

If CD is suspected clinically or individuals are undergoing screening for it, the initial test of choice is serology and immunoglobulin (Ig)A anti-tTG2 assay. This has been shown to have a high sensitivity and specificity – 97% and 96%, respectively. However, it is important that the result is interpreted in the context of the patient's total serum IgA as CD is strongly associated with IgA deficiency. In such circumstances, an IgG anti-TTG antibody assay should be undertaken. Additionally, anti-endomysial antibodies (EMAs) can be used to help confirm the diagnosis, particularly if the tTG2 antibody titre is low.

The UK National Institute for Health and Care Excellence (NICE) recommends that young people and adult patients with positive tTG2/EMA results should be 'referred to a gastrointestinal specialist for endoscopic intestinal biopsy to confirm or exclude coeliac disease' (see Further reading). The situation may be different in children, in whom positive serological tests, appropriate HLA-DQ status and compatible symptoms might be regarded as sufficient to make a diagnosis without undertaking a small bowel biopsy.[3,4] Genetic testing by determining HLA-DQ status is used to support the diagnosis in ambiguous cases but is not routinely used outside specialist centres.

There is a strong genetic contribution to the development of CD, and family members are at increased risk of developing the condition (overall risk approximately 10%). In 2015, NICE recommended that serological testing should be offered to first-degree relatives of patients with CD. Those with symptoms suggestive of CD should then be referred for serological assessment and duodenal biopsies.

Duodenal histology is strongly recommended in adults suspected of having CD. The location, number and orientation of biopsies affects the diagnostic yield. In most cases, mucosal damage is patchy. Biopsy samples should be taken from the distal duodenum (beyond the ampulla of Vater) and the duodenal bulb (as characteristic enteropathy is localized to the duodenal bulb in approximately 13% of patients). The British Society of Gastroenterology (BSG) recommends that at least four biopsies are taken from 'the bulb and the more distal duodenum', to maximize diagnostic accuracy.

Difficulties with diagnosis often arise in situations in which subtotal villous atrophy is associated with negative serology. The differential diagnosis of villous atrophy is wide and needs consideration in ambiguous cases (Table 1).

### Pathology

The classic pathological changes of CD in the small bowel were first described by Marsh in 1992.[5] This was subsequently updated in 1999 by Oberhuber and colleagues, who proposed a new standardized reporting scheme based on the Marsh classification, in which stage 3 was split further into 3a, 3b and 3c. There has been considerable debate surrounding the value and utility of the different systems of classifying the severity of the small bowel damage, but the Marsh system, with or without the Oberhuber modification, remains widely used. A simplified version is shown in Table 2.

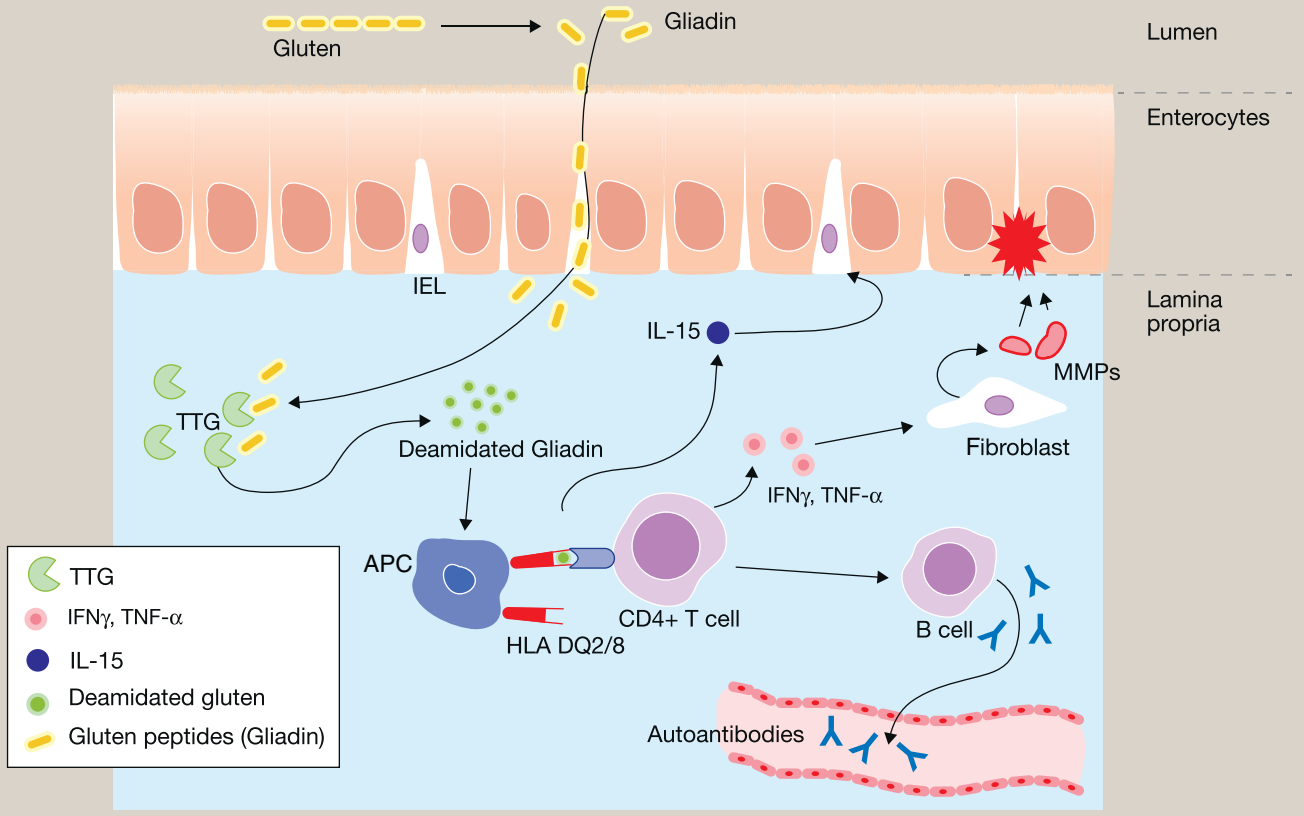
## Treatment

Life-long compliance to a GFD is the only currently recommended treatment for CD. This involves avoiding wheat, rye and barley, which are contained in a wide range of foods consumed by populations in developed countries. Newly diagnosed patients with CD should be referred to a dietician with appropriate experience for education and support in maintaining a GFD.

In the UK, patients are also advised to contact the national charity Coeliac UK (www.coeliac.org.uk), which is 'an independent charity helping people living without gluten to live happier, healthier lives'. Membership ensures that patients are provided with comprehensive up-to-date information on gluten-free products. Perhaps just as importantly, the charity also removes foods from the gluten-free list if production changes result in gluten exceeding 20 parts per million.

Oats contain avenin (a protein similar to gluten), and research has shown that most people with CD can tolerate gluten-free oats. However, oats are frequently produced alongside wheat, barley and rye, and therefore they can become contaminated with these other grains. Only uncontaminated oats can be eaten by people with CD or gluten sensitivity.

## Pathogenesis of the small bowel inflammation seen in CD




Dietary gluten molecules are absorbed across the enterocytes and are deamidated by tTG2 (here denoted as TTG) and presented via HLA-DQ2 or HLA-DQ8 molecules to the CD4+ T cells. This results in the release of cytokines IL-15, interferon-γ (IFNγ) and TNF-α, which result in downstream effector actions. In addition, B cell activation results in the production of autoantibodies to tTG2.

**Figure 2**

## Differential diagnosis of subtotal villous atrophy

- Tropical sprue
- Crohn's disease
- Whipple's disease
- Giardiasis
- Radiation enteritis
- Tuberculosis
- Zollinger–Ellison syndrome
- Collagenous sprue
- Common variable immunodeficiency
- Autoimmune enteropathy
- Eosinophilic gastroenteritis
- HIV enteropathy
- Drug-induced enteropathy, e.g. azathioprine, methotrexate, mycophenolate, olmersatan, colchicine

Before considering a diagnosis of CD, it is important to exclude or at least consider other causes of villous atrophy, especially in individuals without positive serology (tTG2/endomysial antibodies).

**Table 1**

## Marsh–Oberhuber classification of pathological findings in duodenal biopsies of patients with CD

| Marsh Type | IEL/100 enterocytes–duodenum | Crypt hyperplasia | Villi |
|---|---|---|---|
| 0 | <30 | Normal | Normal |
| 1 | >30 | Normal | Normal |
| 2 | >30 | Increased | Normal |
| 3a | >30 | Increased | Mild atrophy |
| 3b | >30 | Increased | Marked atrophy |
| 3c | >30 | Increased | Complete atrophy |

**Table 2**

A proportion of patients have nutritional deficiencies (including iron, calcium and folate) at diagnosis. These require replacement using supplements as the small bowel pathology recovers.

A vast majority of patients respond to a GFD with recovery of small bowel structure and function. However, a small proportion

of patients, despite strict adherence to a GFD, fail to show mucosal healing. This could be the result of slow mucosal recovery (i.e. longer than 1 year) or the development of refractory CD (RCD). RCD is defined by the absence (type I) or presence (type II) of increased numbers (>20%) of intraepithelial lymphocytes (IELs) with an abnormal phenotype (characterized by an absence of cell surface CD3 expression but with CD3 contained in the cytoplasm). IELs with absent, or significantly reduced, CD3 expression are considered lymphoma precursor cells. In some studies, >50% of patients with type II RCD developed overt lymphoma within 5 years. The distinction between type I RCD and a slow response to a GFD can be a challenge in clinical practice.

## Survival

Several papers have addressed survival in patients with CD. For example, 100 patients were followed up in Denmark for 18 years. In this cohort, the standardized mortality ratio (SMR; the ratio of observed to expected deaths) was 3.4 compared with the general population ($p < 0.025$). Apart from an increased risk of mortality from malignancy, there was also a high death rate from suicide (three deaths), diabetes mellitus (five deaths) and inflammatory bowel disease (two deaths) (see Neilsen et al. in Further reading). A Scottish group found an SMR of 1.9 in 653 patients with CD (95% confidence interval (CI) 1.5–2.2; $p < 0.001$). The increased mortality was observed principally in the first year of diagnosis of CD in 45–65-year-old patients and was mostly related to the development of lymphomas.

The most robust study on mortality in recent years was based in Italy. A cohort of 1072 patients with CD and another of 3384 first-degree relatives were followed up for about 35 years from diagnosis and the expected mortality was compared. In the group with coeliac disease, the SMR was 2.0 (95% CI 1.5–2.7). A significant excess of mortality was seen in the first 3 years after diagnosis and in patients who presented with malabsorption (SMR 2.5, 95% CI 1.8–3.4), but not in those who presented with minor symptoms (SMR 1.1, 95% CI 0.5–2.2), or who were asymptomatic and were diagnosed after antibody screening (SMR 1.2, 95% CI 0.1–7.0). Mortality was high (SMR 3.8, 95% CI 2.2–6.4) in patients in whom the diagnosis was delayed for >10 years after the onset of symptoms, but highest in patients not adherent to a GFD (SMR 6.0, 95% CI 4.0–8.8). There was no increased mortality in the relatives of patients with CD. The increased mortality seen in patients with CD was mainly caused by malignancy, with an excess of deaths from non-Hodgkin's lymphoma (see Corrao et al. in Further reading).

Most available data therefore point towards a decreased life expectancy in individuals diagnosed later in life, with severe symptoms and failing to adhere to a GFD. However, whether most people with CD who remain undiagnosed in the community and are not following a GFD have a normal or reduced life expectancy is not yet clear.

## Associated conditions

CD is an autoimmune disorder and is associated with numerous other autoimmune diseases as well as other apparent non-immune conditions. Patients with CD should be screened for many of these disorders at diagnosis in the appropriate clinical setting. Table 3 includes conditions reported in the literature as being associated with CD. For many of these, however, the mechanism of the association is unclear.

## Special situations

### Dermatitis herpetiformis

Dermatitis herpetiformis is an intensely pruritic bullous skin rash of the extensor surface of the limbs, trunk and scalp. It is an example of an extraintestinal form of CD. Patients with dermatitis herpetiformis have IgA tTG2 (80–95% of cases), HLA-DQ2 (90%) and villous atrophy (75%, the remaining 25% demonstrating increased IELs) and respond to a GFD. However, these individuals are often treated with dapsone rather than a GFD.

### Osteoporosis

The risk of osteoporosis and bone fracture is increased in patients with CD. The excess risk appears to be reduced in individuals who adhere to a GFD and who recover from the villous atrophy seen in CD.

Bone density should be measured in those at high risk of osteoporosis. Assessment of fracture risk should be considered in all women aged 65 years and over, and all men aged 75 years and over. Women <65 years old and men <75 years should be

### Conditions that have been associated with CD in the literature

**Autoimmune conditions**
- Autoimmune thyroid disease
- Type 1 diabetes mellitus
- Addison's disease
- Sjögren's syndrome
- Juvenile idiopathic arthritis

**Hepatological conditions**
- Autoimmune hepatitis
- Primary biliary cholangitis
- Primary sclerosing cholangitis
- Wilson's disease
- Budd–Chiari syndrome

**Dermatological conditions**
- Dermatitis herpetiformis
- Vitiligo
- Dermatomyositis
- Psoriasis

**Miscellaneous conditions**
- Sarcoidosis
- Dilated cardiomyopathy
- Idiopathic thrombocytopenic purpura
- Immunoglobulin A deficiency
- Epilepsy and occipital calcification
- Pancreatitis
- Hyposplenism

**Chromosomal abnormalities**
- Turner's syndrome
- Down's syndrome
- William's syndrome

**Table 3**

assessed taking into account the presence of risk factors, for example previous fragility fracture, current or frequent recent use of glucocorticoids, history of falls, family history of hip fracture, causes of secondary osteoporosis, low body mass index (<18.5 kg/m$^2$), smoking and alcohol intake of >14 units/week. Fracture risk is not routinely required in those aged <50 years unless they have major risk factors (e.g. high exposure to glucocorticoids, premature menopause, previous fragility fracture) as they are unlikely to be at high risk. There are numerous methods of fracture risk assessment including algorithm-derived models (e.g. FRAX®, QFracture®), and bone mineral density using dual-energy X-ray absorptiometry (DEXA). Most patients referred by gastroenterologists for fracture risk assessment undergo a DEXA scan.

Adult patients with CD should have a calcium intake of at least 1000 mg/day. In individuals who are found to have reduced bone density, or who have evidence of continuing villous atrophy or poor dietary adherence, a repeat bone density investigation (generally after an interval of 2 years or more) should be considered. Postmenopausal women with CD can require supplementation in addition to the GFD. Further bone loss despite adherence to a GFD should prompt measurement of vitamin D levels, dietary review of adherence and consideration of repeat intestinal mucosal biopsy.

### Non-coeliac gluten sensitivity (NCGS)

NCGS is a clinical syndrome of intestinal and extraintestinal symptoms related to the ingestion of gluten-containing foods in individuals who are not affected by CD or wheat allergy. Controversy still surrounds this clinical diagnosis because although NCGS seems to be triggered by gluten-containing cereals, the specific offending dietary protein has not yet been identified, and could include non-gluten related peptides such as the cereal protein amylase–trypsin inhibitors. The prevalence of NCGS is difficult to accurately define, and evidence suggests that NCGS might be more common than CD. The treatment of NCGS is currently a GFD, although whether this is necessary or sufficient to control symptoms in all patients is unknown. Many clinicians dispute the existence of NCGS in the absence of definable and measurable changes in the appearance of the small bowel mucosa. Future research will better clarify the position of NCGS among the gluten sensitivity disorders.

## Future developments

The treatment of CD is life-long compliance to a GFD. However, for many patients, economic and other societal pressures prevent strict compliance, often resulting in recurrent villous atrophy and harmful effects on overall general health. Many biotechnology companies worldwide are engaged in clinical trials of compounds that could soon find their way into the clinical setting. This includes drugs targeted to inhibit the toxic potential of gluten, an antibody that inhibits the cytokine interleukin (IL)-15 (which plays multiple roles in the immune system of the gastrointestinal tract), inhibitors of HLA-DQ2 and HLA-DQ8, and treatments targeting tTG2. Finally, a peptide-based therapeutic vaccine has been developed to prevent and treat immune diseases for multiple sclerosis, type 1 diabetes mellitus, rheumatoid arthritis and other autoimmune diseases including CD. ◆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### FURTHER READING

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# TEST YOURSELF

To test your knowledge based on the article you have just read, please complete the questions below. The answers can be found at the end of the issue or online here.

### Question 1

A 20-year-old woman presented with a 12-month history of abdominal bloating, change in bowel habit, a 5-kg weight loss and vitamin $B_{12}$ deficiency. Despite treatment with vitamin $B_{12}$, she remained symptomatic.

**Investigation**

- Tissue transglutaminase 2 (tTG2) immunoglobulin A antibody-positive (titre >120 U/ml) (<10.0)

**What should the subsequent management plan include?**

A. Immediately start a gluten-free diet
B. Refer for an endoscopy and duodenal biopsies
C. Check HLA status and commence a gluten-free diet if DQ2 heterodimers are positive
D. Refer for a bone density scan
E. Refer for capsule endoscopy to detect changes of villous atrophy

### Question 2

A 58-year-old man presented with a 2-month history of watery diarrhoea. He had a long history of ischaemic heart disease, intermittent claudication and hypertension. He was taking aspirin, olmersartan, furosemide, lansoprazole and bisoprolol.

**Investigations**

- Faecal calprotectin 150 micrograms/g stool (<30)
- tTG2 antibody 1.4 U/ml (0–2.4)
- Small bowel histology demonstrated villous atrophy and increased numbers of intraepithelial lymphocytes

**What is the most likely diagnosis?**

A. tTG2-negative coeliac disease
B. Small bowel Crohn's disease
C. Olmersartan-induced enteropathy
D. Non-steroidal anti-inflammatory drug enteropathy
E. Ischaemic colitis

### Question 3

A 65-year-woman presented with increasing weight loss, abdominal pain and diarrhoea. Twelve months previously, she had been found to have coeliac disease. The diagnosis had been based on positive tTG2 antibody and small bowel villous atrophy. After an initial symptomatic improvement, she had now relapsed.

**Investigations**

- Haemoglobin 94 g/litre (115–165)
- Repeat tTG2 antibody negative
- Repeat small bowel histology demonstrated partial villous atrophy

**Which are the most appropriate next investigations?**

a) Colonoscopy and biopsy
b) CT of the thorax, abdomen and pelvis
c) Capsule endoscopy
d) Repeat duodenal biopsies and examination for CD3 expression
e) Laparoscopy and full-thickness biopsy