Celiac disease: diagnosis and treatment

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INTRODUCTION

Celiac disease (CD) is a chronic, immune-mediated enteropathy of the small intestine. In genetically predisposed individuals, it is triggered by gluten in food products [1,2]. Left untreated, CD may cause malabsorption, reduced quality of life, iron deficiency, and osteoporosis, and there is an increased risk of lymphoma. The disease prevalence is 0.5-1.0%, but CD remains under-diagnosed. Clinically, CD presents with a broad spectrum of symptoms, with or without malabsorption. Knowledge of classical and non-classical symptoms, as well as access to an appropriate diagnosis and counselling, are all crucial for the patients’ prognosis. The disease is associated with several autoimmune diseases, most importantly diabetes mellitus type 1.

The diagnosis of CD is made by the presence of characteristic histopathological changes in duodenal biopsies in the form of crypt hyperplasia and villous atrophy, as well as by the remission of clinical symptoms and improved histology while the patient is on a gluten-free diet (GFD). The presence of CD antibodies and specific HLA (human leukocyte antigen) haplotypes may aid the clinical evaluation [3,4]. Patients with atypical symptoms and inconsistency between serology and histology can be a diagnostic challenge.

The treatment for CD is a lifelong GFD, which, in the majority of patients, normalises the small intestinal mucosa and absorption.

The adherence to a GFD usually requires dietary advice from a clinical dietician. The monitoring of antibody levels and malabsorption markers allows for early treatment of disease complications.

Terminology

CD can be divided into different clinical phenotypes. We recommend the following terminology used by Ludvigsson et al. [5].

- Classical CD: Malabsorption syndrome with micronutrient deficiency, which is dominated by diarrhoea, fatigue, and weight loss. It often includes muscle weakness, muscle and bone pain, glossitis, aphthous stomatitis, and tooth enamel defects, and possibly lactose malabsorption. The patient’s biochemistry is usually affected.

- Non-classical CD: This condition is characterised by no or few gastrointestinal symptoms (e.g., abdominal pain, constipation, flatulence, and dyspepsia); however, extraintestinal manifestations are predominant (e.g., dermatitis herpetiformis, selective IgA deficiency, autoimmune liver diseases, diabetes mellitus type 1, autoimmune endocrine disorders (thyroiditis), certain neuropsychiatric disorders, osteopenia, and infertility).

- Symptomatic CD: The presence of gastrointestinal or extraintestinal symptoms due to gluten ingestion.

- Asymptomatic CD: This condition is found in asymptomatic individuals or people with vague complaints, such as fatigue, which can only be identified after starting a GFD (the latter group can be described as having subclinical CD).

- Potential CD: This condition is found in asymptomatic individuals with positive CD serology but with normal small intestinal histology. These individuals are considered at risk for later development of symptoms and/or mucosal lesions. This group can be difficult to differentiate from individuals with asymptomatic CD, because mucosal lesions in the proximal small intestine may be sporadic and patients’ habitual gluten intake may vary.

- Refractory CD: Refractory CD is defined as persistent or recurrent symptoms (typically diarrhoea and weight loss) and signs of malabsorption that are accompanied by villous atrophy despite a strict GFD for at least 12 months and in the absence of other conditions.

The terms typical CD, latent CD, gluten intolerance, gluten sensitivity, and gluten allergy are not recommended [5].
Follow-up of CD patients

- Adherence to a GFD should be monitored through antibody measurements and interviews regarding dietary intake
- Follow-up of CD patients should include biochemical control of vitamin and mineral deficiencies
- Persistently elevated transglutaminase in patients with CD is the leading cause of non-adherence to a GFD
- Patients with newly diagnosed CD should be referred for a bone mineral density test (DXA scan)

See the flow charts below for the follow-up protocol for CD patients

Table 1. Quick guide to the diagnosis and treatment of celiac disease (CD) in adults.

Who should be tested for CD?

- **Absolute indications**
  - Symptoms or clinical findings that are consistent with classical CD
  - Unexplained iron-deficiency anaemia
  - Dermatitis herpetiformis
  - First-degree relative of CD patient

- **Relative indications**
  - Diabetes mellitus type 1
  - Elevated transaminases without a known cause
  - Osteopenia/osteoporosis
  - Autoimmune disorders (e.g. sarcoidosis, Sjogren’s syndrome, autoimmune liver disease, and Addison’s disease)
  - Down's syndrome and Turner’s syndrome
  - Irritable bowel syndrome
  - Neurological disorders (e.g. polyneuropathy of unknown cause and epilepsy)
  - Unexplained infertility
  - Second-degree relative of CD patient
  - Microscopic colitis
  - Aphthous stomatitis and tooth enamel defects

How to diagnose CD?

- Patients with a strong clinical suspicion of CD should be examined with both antibody measurements and duodenal biopsies
- Patients with a low clinical suspicion can be tested for CD with antibody measurements alone
- A positive antibody result should always be supplemented with duodenal biopsies
- IgA anti-transglutaminase (IgA anti-TG2) combined with measurement of total IgA in serum or IgG anti-deamidated gliadin peptide (IgG anti-DGP) are the recommended antibody measurements
- Antibody measurements and duodenal biopsies must be obtained when the patient is on a gluten-containing diet
- ≥ 4 biopsies from the duodenum and ≥ 1 biopsy from the duodenal bulb are recommended
- The absence of haplotypes HLA-DQ2 and HLA-DQ8 excludes CD

Treatment of CD

- Treatment of CD is a lifelong GFD
- All patients with confirmed CD should be offered dietary guidance by a clinical dietician
- Vitamin and mineral levels in the plasma should be measured and substituted until normalisation

Comments regarding the absolute indications

International guidelines and reviews agree that patients with symptoms and findings consistent with classical CD should be tested for CD [1,3,6].

Unexplained iron-deficiency anaemia is associated with CD, irrespective of the presence of gastrointestinal symptoms [7-9]. In patients with unexplained iron-deficiency anaemia following upper and lower endoscopies, CD prevalence rates between 8.7% and 14.6% have been reported [7-9]. CD should be considered in all patients with unresolved anaemia, and it is recommended to...
perform duodenal biopsies in all of these patients as part of the diagnostic work-up [6,8]. Dermatitis herpetiformis is a cutaneous manifestation of CD, and all patients with dermatitis herpetiformis should be examined for CD [10,11]. First-degree relatives to CD patients carry a significantly increased risk of CD, with prevalence rates between 4.5% and 11% and they should be screened for CD [12,13]. The CD prevalence is lower (2.5%) among second-degree relatives. Negative serology in these individuals may induce a false sense of security because CD may still develop later in life.

Comments regarding the relative indications
Patients with non-classical CD may be monosymptomatic or present with various gastrointestinal or extraintestinal symptoms. Although this form of CD used to be relatively rare, the proportion of patients who present without diarrhea, decreased body weight, and malabsorption has increased, and non-classical CD is now a frequent presentation form [14]. The threshold for testing individuals presenting with non-classical symptoms should be low [12,15].

CD is associated with an increased risk of autoimmune diseases, most importantly diabetes mellitus type 1, which is associated with CD in 2.5–7% of cases [12,16,17]. CD is also associated with autoimmune liver diseases [18]. Elevated transaminases are seen in more than 20% of patients with newly diagnosed untreated CD without evidence of significant liver disease in general. The reason for this hepatic effect is unknown; however, increased transaminases normalise in the majority of patients on a GFD [19]. Patients with unexplained transaminasaemia were, in a meta-analysis, found to have a 4-fold increased risk of having underlying CD [19]. Several other autoimmune, genetic, and neurological diseases are associated with CD (prevalence 2–6%), and investigation of patients who present without diarrhoea, decreased body weight, and malabsorption has increased, and non-classical CD is now a frequent presentation form [14]. The threshold for testing individuals presenting with non-classical symptoms should be low [12,15].

How to DIAGNOSE CD?

- Patients with a strong clinical suspicion of CD should be examined with both antibody measurements and duodenal biopsies. Patients with a low clinical suspicion can be tested for CD with antibody measurements alone (GRADE A).
- A positive antibody result should always be supplemented with duodenal biopsies (GRADE A).
- IgA anti-transglutaminase (IgA anti-TG2), coupled with total serum IgA or IgG anti-deamidated gliadin peptide (IgG anti-DGP), are the recommended antibody measurements (GRADE A).
- Antibody measurements must be performed before the patient starts a GFD (GRADE B).
- The number of biopsies should be ≥4 from the duodenum and ≥1 from the duodenal bulb (GRADE A).
- The absence of the HLA-DQ2 and HLA-DQ8 haplotypes excludes CD with high probability (GRADE B).
- Capsule endoscopy can be used as an alternative diagnostic modality in selected patients with clinically and serologically suspected CD where gastroscopy cannot be performed (GRADE A).

Comments regarding clinical suspicion
Because antibody measurements are not 100% sensitive, patients with a strong clinical suspicion of CD, i.e. patients with symptoms compatible with classical CD, should always be further evaluated with duodenal biopsies, regardless of the antibody test outcome [1-4,21]. However, patients with a low clinical suspicion can, however, be screened for CD with antibody testing alone. If the antibody test is positive, it is recommended to proceed to upper endoscopy with duodenal biopsies [1-4,21].

Comments regarding pathology
The histological changes in CD are non-specific and are associated with many different diagnoses; however, duodenal biopsies remain central in the diagnosis of CD in adults. The changes in the small intestinal mucosa can vary from a slightly increased number of intraepithelial lymphocytes to crypt hyperplasia and complete villous atrophy. The histological changes can be classified according to the modified Marsh classification (Marsh Oberhuber) [22], which is the classification most commonly used among Danish pathologists (Table 3).

The histological changes may be focal [23,24]. To increase the diagnostic yield, a minimum of 4 biopsies should be taken from the duodenum if there is suspicion of CD [25,26]. Several studies have demonstrated that in children and adults with positive CD serology, additional biopsies from the duodenal bulb increase the diagnostic yield, particularly in patients with focal changes [24,27-34]. In these studies, villous atrophy was restricted to the duodenal bulb in up to 13%. Currently, no evidence supports that taking bulb biopsies increases the diagnostic yield in patients with negative serology. In biopsies from the duodenal bulb, many Brunner glands are observed, villi are shorter, and peptic changes are frequently observed, which can result in histopathological changes that overlap with CD. Hence, the pathologist should be informed that duodenal bulb biopsies have been performed.

Intraepithelial lymphocytosis and villous atrophy are not specific to CD. Marsh I changes (intraepithelial lymphocytosis with normal villous architecture) can also be seen in Helicobacter pylori infections, giardiasis, peptic duodenitis, bacterial overgrowth, tropical sprue, consumption of non-steroidal anti-inflammatory drugs (NSAIDs), Crohn’s disease, and autoimmune diseases (e.g. rheumatoid arthritis, immunoglobulin A deficiency, and chronic variable immunodeficiency syndrome). The same conditions can result in villous atrophy [35]. Therefore, the histological changes are not independently diagnostic and must always be combined with the serology and clinical findings. In case of inconsistency between serology and histology, including the presence of minor histological changes (Marsh 1-2), other diseases than CD should be considered.

Comments regarding CD specific antibodies
CD-specific antibody measurements mainly include IgA anti-transglutaminase (IgA anti-TG2), which is combined with total serum IgA or IgG anti-deamidated gliadin peptide (IgG anti-DGP) measurements. Endomysium antibody (EMA) may be performed in special cases in some laboratories. The sensitivity and specificity are similar to those of the above-mentioned analyses; however, it is no longer recommended for use in clinical practice because it is expensive and semi-quantitative.

IgA anti-TG2: The diagnostic sensitivity and specificity of IgA anti-TG2 are 90-95% [36-38]. The titre does not necessarily reflect the degree of histological changes, although high IgA anti-TG2 titres (more than 5 times the reference value) mainly occur in patients with Marsh 3 histopathology [39,40].

IgG anti-DGP: The diagnostic value of IgG anti-DGP is comparable to that of IgA anti-TG2 [37,41].

The positive and negative predictive values of serological testing vary depending on the patient groups studied. In populations with a low CD prevalence, the positive predictive value is low.
Hence, a diagnosis of CD should be based on elevated levels of CD specific antibodies combined with clinical data and histology.

Comments regarding HLA haplotypes
CD is strongly associated with HLA-DQ2 and HLA-DQ8, and it is estimated that > 95% of CD patients carry one of these HLA haplotypes (HLA-DQ2 90% and HLA-DQ8 5%) [42-44]. HLA-DQ2 and HLA-DQ8, however, occur in 30-40% of the general population. Therefore, a positive test result is not diagnostic for CD (low specificity) [42,45,46]. Importantly, the absence of HLA-DQ2 and HLA-DQ8 excludes CD with a high probability. In a prospective study of 463 patients with suspected CD who had an upper endoscopy, HLA DQ2/8 genotyping had a sensitivity and negative predictive value of 100% (prevalence 3.46%) [46]. HLA typing did not increase the test performance compared with that of serological testing alone. Hence, HLA-DQ2/8 genotyping can be used as complementary analysis in situations where there is doubt regarding the diagnosis, e.g. in patients with a discrepancy between serology and histology or in patients started a GFD prior to the diagnostic assessment.

Comments regarding the investigations
If a patient already began a GFD before the investigation, negative serology and normal histology may not exclude CD [47,48]. Renewed serological and histological examinations after gluten provocation should be considered. In these cases, HLA typing before gluten provocation may be informative because the absence of HLA-DQ2/8 obviates the need for further CD investigation.

There are virtually no data regarding the optimal gluten dose and length of exposure necessary to exclude the diagnosis. Traditionally, 10 g of gluten per day for 6-8 weeks has been recommended prior to re-examination [3]. Ten grams of gluten corresponds to approximately 3 slices of white bread, with one slice of white bread (50 g) containing approximately 30 g of flour, which contains approximately 10% (3 g) gluten. In a recent study, even a small dose of gluten (≥3 g/day) resulted in histological changes and/or increasing antibody titres in 85% of the subjects after 2 weeks and 90% after 4 weeks [49]. It is unknown whether the sensitivity increases further by continuing gluten exposure.

Comments regarding capsule endoscopy
Reduced or absent villous height, nodular mucosa, scalloping, fissures, mosaic pattern, loss of mucosal folds, and visible blood vessels are characteristic endoscopic findings in CD [50].

Capsule endoscopy has a high sensitivity for the diagnosis of villous atrophy. In a meta-analysis of six studies with a total of 166 patients who were tested for CD, capsule endoscopy had a sensitivity of 89% and a specificity of 95% [51]. There was a moderate to high interobserver agreement (kappa 0.49 to 1.0). Capsule endoscopy can be used as an alternative diagnostic modality in selected patients with clinical and serological suspicion of CD where gastroscopy cannot be performed.

Whether capsule endoscopy can aid in the diagnosis in patients with a discrepancy between serology and histology is not clear. In patients with clinically suspected CD without villous atrophy (Marsh 0-2), the diagnostic yield of capsule endoscopy was low (0-7%) [52,53]. However, it seems that capsule endoscopy adds significant diagnostic information in a proportion of patients with clinical suspicion of CD and antibody-negative villous atrophy [53].

How should CD be treated?
- The treatment for CD is a lifelong GFD (GRADE A).
- All patients with confirmed CD should be offered dietary guidance by a clinical dietician (GRADE D).
- Oats are tolerated by most CD patients (GRADE B).
- Oat products may be contaminated with wheat; therefore, pure oats are recommended (GRADE B).
- Vitamin and mineral plasma levels should be measured and substituted until normalisation (GRADE B).

Comments regarding the GFD
The treatment for CD is a lifelong GFD, which improves symptoms, quality of life, nutrition, and body composition in most patients [54-58]. Both serological [19] and histological changes improve with a GFD [59]. The GFD has a documented effect on several biochemical markers of malabsorption, including iron absorption and haemoglobin [7,9]. Additionally, bone mineral density (BMD) increases [60-62]. The increased risk of infertility, intrauterine growth retardation, low birth weight, and preterm delivery, which are seen in untreated CD, normalises [6,63,64].

All patients with newly diagnosed CD should be referred for dietary guidance from a clinical dietician with experience in adressing celiac patients. Counselling aims to improve adherence to a GFD and ensure adequate intake of protein, whole grains, fibre, iron, vitamins, and minerals.

The immunogenic gluten fractions in gluten (prolamins) are found in wheat (gliadin), rye (secalin), and barley (hordein), with the highest concentrations occurring in wheat. Spelt, einkorn, ancient wheat species, durum, and other wheat varieties all contain gluten. The limits of a declared GFD are defined by the World Health Organization (WHO) in the Codex Alimentarius (www.codexalimentarius.org). Food items that are labelled as gluten-free may contain up to 20 mg gluten/kg. Food items that are labelled as having “very low gluten” may contain up to 100 mg gluten/kg. Generally, the labelling of gluten-free food in Europe is valid [65]. The lower limit of immunogenic gluten exposure is not well defined and varies from person to person; however, a daily intake of up to 10 mg of gluten is considered safe [66].

Oats constitute a major source of whole grains, fibre, vitamin B, magnesium, and iron [67]. The intake of oats should not be limited in CD patients because the prolamin that is contained in oats, avenin, is not immunogenic in the vast majority of CD patients [68-71]. Oat products may, however, be contaminated with wheat [72], and CD patients should only consume certified gluten-free oats (pure oats).

Beer contains gluten in varying concentrations, and the concentration is highest in beer made of wheat [73,74]. Beer without a declaration of gluten content is not recommended. Certified gluten-free beer can be consumed.

Comments regarding vitamin supplements
Vitamin deficiencies occur with increased frequency in patients with untreated CD [75,76]. A GFD in itself is a risk for low intake of whole grains, dietary fibre, and B vitamins [76-78]. Plasma levels of 25-hydroxy vitamin D2 + D3, ferritin, folate, and cobalamin should be measured. Insufficiencies should be treated according to standard protocols, and plasma levels should be monitored until normalisation. If normalisation of plasma levels is not obtained by oral treatment, parenteral administration should be considered. Other deficiencies that may occur in CD include retinol (vitamin A), vitamin C, magnesium, copper, and zinc [76].
Comments regarding enzyme supplements
In case of lactose malabsorption secondary to CD, lactase supplementation or lactose-free products are recommended. A clinical dietician should offer advice regarding lactose-containing products.

Comments regarding medical treatment
Additional medical treatment for early CD has been attempted, particularly with corticosteroids, including budesonide [79-81]. Larazotide acetate inhibits gluten absorption and may reduce immunogenicity in diagnosed CD patients [82,83]. The evidence for a medical treatment effect is scarce, and medical treatments for CD are currently not recommended.

Osteopenia/osteoporosis
- Patients with classical CD should be offered a BMD scan (DXA) at diagnosis (GRADE B), and levels of ionised calcium, 25 (OH) D2 + 3, and PTH should be determined.
- Treatment for osteopenia/osteoporosis in CD is a GFD (GRADE A) and adequate calcium and vitamin D supplementation. In the presence of osteoporosis secondary to CD and in the absence of other risk factors, anti-resorptive medications may be postponed. In patients with multiple risk factors, immediate anti-resorptive therapy should be initiated. For further guidance, refer to the Danish Bone Society: Guide to assessment and treatment of osteoporosis.
- Patients with decreased BMD at diagnosis should be offered a control DXA scan after 1 year of treatment with a GFD (GRADE B).

Comments regarding osteopenia/osteoporosis
Two large studies, a national register study and a systematic review, revealed that the risk of fracture is doubled in CD patients [84,85]. In general, BMD is significantly reduced in patients with CD compared with healthy controls [61,86]. Reduced BMD is more frequent among celiac patients with the presence of other risk factors for osteoporosis, such as advanced age, smoking, low BMI, and early menopause [61,86]. Patients with classical CD have significantly lower BMDs and more fractures than patients with non-classical and asymptomatic CD [86,87]. The prevalence of osteoporosis in CD is uncertain and varies from 14-35% [60,86,88]. Several studies have demonstrated an increase in BMD after starting a GFD [60-62], with the largest increase observed in the first year [62]. Although the documented benefits of DXA are greatest in patients with classical CD and/or the presence of other risk factors for osteoporosis, we recommend that all patients with newly diagnosed CD are offered a BMD scan, clinical and serological follow-up, and appropriate medical therapy, according to the flow chart: “Follow-up of newly diagnosed CD”.

Follow-up in celiac disease
- Compliance with a GFD should be monitored by a diet interview and/or food registration and antibody measurement (GRADE B).
- The follow-up of patients with CD should include biochemical control of vitamin and mineral deficiencies (GRADE C).
- Persistently elevated transglutaminase levels in patients with CD are most often caused by insufficient adherence to a GFD (GRADE B).
Comments regarding follow-up

CD patients should be followed in order to assess the effect of GFD on symptoms and malabsorption, [59,89,90] facilitate adherence to a GFD and prevent or diagnose complications. Adherence to a GFD is seen in 40-90% of all CD patients [91,92] and is associated with socioeconomic factors [91,93]. Low adherence increases the risk of complications and a reduced quality of life [94]. Non-adherence is the leading cause of persistently elevated transglutaminase levels and should be suspected before refractory CD is diagnosed [95]. Specific patient education programs may increase adherence [96,97], but clear recommendations regarding the nature of such programs cannot yet be given.

Antibody measurements are also used to measure the effect of a GFD [59,90,98,99]. After the initiation of a GFD, the antibody titres drop steeply and are expected to become normal in half of the patients after approximately three months and in 80-90% after one year [100,101]. A positive titre after two years suggests non-adherence with a GFD. The serological improvement is not parallel with the histological healing, which is slower. Normal antibody titres can be seen during the intake of low gluten amounts, and a normal antibody titre cannot be taken as evidence of histological healing [102-104].

Biopsies from the duodenum as part of monitoring or verification of adherence to a GFD are not recommended as routine [3,6] but may, however, be relevant in selected patients with persistent or recurrent symptoms (refractory CD).

There are no systematically collected data to support a specific follow-up frequency for CD patients. In general, annual follow-ups are recommended [3,59]. The guideline group recommends that stable CD patients are offered annual clinical and biochemical follow-up by a dedicated therapist (see flow chart in the quick guide).

Refractory CD

- When refractory CD is suspected, patients should be offered a repeat upper endoscopy with duodenal biopsies for a new histological and immunohistochemical assessments (GRADE A).
- Refractory CD, type I may be treated with corticosteroids, budesonide, mesalamine, thiopurines, cyclosporine, or infliximab (GRADE C).
- In patients with unresolved refractory CD capsule endoscopy can be performed (GRADE C).

Comments regarding refractory CD

Refractory CD (RC) is defined as persistent or recurrent symptoms (typically diarrhoea and weight loss) and signs of malabsorption that are accompanied by villous atrophy despite a strict GFD for at least 12 months and in the absence of other conditions; thus, it is an exclusion diagnosis in clinical practice.

RC is estimated to affect 1% to 4% of patients with CD and is generally diagnosed in patients over 50 years of age, most frequently in males [1,3,105,106]. RC is divided into Type I, characterised by normal intraepithelial lymphocyte levels (as in untreated CD), and Type II, characterised by 20% or more aberrant monoclonal intraepithelial lymphocytes with non-expression of surface T-cell marker antigens, including CD3, CD4, CD8, and the T-cell receptor [1,107]. In a recent Finnish report, RC accounted for 0.3% of patients who were diagnosed with CD, less than a quarter of whom had RC type II [106]. Both RC types are associated with an increased risk of lymphoma. The 5-year survival rate for patients with RC Type II is significantly lower (below 50%) than that for patients with RC Type I, mainly due to lym-
phoma development, which is seen in up to half of RC Type II patients after 5 years [1,108].

If RC is suspected, the CD diagnosis should be reconsidered, especially if lymphoma and diet non-adherence are excluded. Patients should be offered a repeat upper endoscopy with duodenal biopsies for histological and immunohistochemical evaluation, verification of the diagnosis, typology, and prognostication [3]. If lymphoma is suspected, an 18F-FDG PET CT scan should be performed (see below). Capsule endoscopy may be helpful in patients with unresolved RF. Capsule endoscopy enables visualisation of the extent and severity of villous atrophy, ulcerative jejunitis, and lesions that are suspicious for enteropathy-associated T-cell lymphoma (EATL). The yield of capsule endoscopy appears to be higher in patients with RC Type II than in those with RC type I [109,110].

There are no randomised clinical trials evaluating medical treatment of either RC Type I or Type II. Small case series have reported varying positive effects of steroids, thiopurines, and combinations thereof, as well as cyclosporine, infliximab, budesonide, and mesalamin in patients with RC Type I [1,3]. For RC Type II, no treatments have known effects, and these patients should be managed in collaboration with a haematologist. There are no systematically collected data to support a particular monitoring strategy. The treatment for both RC types is otherwise symptomatic and includes supportive nutrition.

**CD and intestinal lymphoma (enteropathy-associated T-cell lymphoma, EATL)**

- An 18F-FDG PET CT scan is recommended for the investigation of EATL in patients with refractory CD (GRADE B).

**Comments regarding EATL**

CD is associated with an increased risk of malignant non-Hodgkin’s lymphoma (NHL) (2-6-fold higher frequency), particularly the EATL type (8-32-fold higher frequency). EATL most frequently occurs in the proximal jejunum, and may be multifocal and ulcerative [111-115]. The EATL incidence in Western countries is equivalent to 3-6 cases per year in Denmark. EATL is most frequently diagnosed in patients above 60 years of age. Men are affected more frequently than women [116]. The disease has an aggressive course with a 5-year survival rate of 8-20% [117]. In older studies, the EATL risk has been found to be reduced to background level after 5 years of a GFD [118]. More recent studies did not find an association between a GFD and the risk of EATL; however, B-cell lymphoma occurred more frequently in patients who were non-adherent to their GFD [119]. CD patients with persistent villous atrophy 0.5-5 years after diagnosis appear to be at the highest risk for developing lymphoma [120]. EATL should be suspected in the presence of refractory CD or alarm symptoms in previously stable CD patients. Screening of refractory CD patients for EATL includes an 18F-FDG PET CT scan, which is more sensitive and specific than contrast-enhanced CT scans [121]. There are no published protocols or recommendations for EATL screening in general.

**Special considerations**

**Malignancies**

Most studies addressing CD and malignancies were performed in small centres or report on small patient samples, resulting in large confidence intervals and uncertain risk estimates. The increased risk of NHL (see above) has been reported repeatedly, and several studies have found an increased risk of developing other cancers, especially in the gastrointestinal tract. The relative risk appears to be related to the patient population, illness duration, and disease severity [122]. Some studies have demonstrated an increased risk of gastrointestinal malignancy, particularly the first year after diagnosis [123-127]; however, this result was not found in studies with longer follow-ups and may reflect a surveillance bias [127]. Two large studies and a meta-analysis, however, examined the overall cancer risk, including the risk for developing lymphoma [115,123,127]. Both the Swedish and British study found a relative risk of approximately 1.3. The meta-analysis included a total of 3 studies (including the British) and found no association between CD and malignancy (odds ratio [OR] 1.07 [95% confidence interval [CI] 0.89 to 1.29]). Why the overall risk of malignancy (including NHL) was not significantly increased when there was also a clear increased risk of NHL is not yet known. Several studies have shown a reduced risk of breast cancer [123,125,126,128,129]; however, this is unlikely to be the only explanation of the lower overall relative risk.

There is no evidence that GFD protects against cancer development. The studies are small and their results inconclusive.

**Mortality**

Several studies have shown an increased mortality in patients with CD, but as a whole the data are inconclusive. The studies are difficult to compare because the study designs and patient populations vary considerably. Previous studies showed a 2-fold increased risk of death, especially in patients with a severe clinical disease course [130,131]. More recent population-based studies only found a slightly increased risk (hazard ratio [HR] approximately 1.3) [132-134]. A meta-analysis, which included 5 studies, revealed a similar increase in mortality, with a pooled OR of 1.24 (95% CI 1.19 to 1.30) [115]. In the meta-analysis, the risk was lowest in the studies with short follow-ups, which can lead to an underestimation of the risk. The increased mortality was mostly due to malignant and cardiovascular diseases [131,133,135-137].

**Hyposplenism**

Increased susceptibility to infections and reduced immunity to certain bacterial groups, together denoted as hyposplenism, has been described in CD patients. In particular, there seems to be an increased frequency of pneumococcal infections [138]. We find that the data do not warrant a general recommendation of pneumococcal vaccination in CD patients.

**Venous thromboembolism**

Hypercoagulopathy with elevated homocysteine levels and low vitamin K-dependent anticoagulant protein (protein C and S) levels are well described in CD patients [139,140]. This feature, combined with the chronic inflammation and autoimmunity characteristics of the disease, has led to a presumption of an increased risk of venous thromboembolic disease. The results of major observational studies are heterogeneous [141-143]. A recently published, Danish, population-based, case-control study is the largest to date. The authors found no overall increased risk of venous thromboembolic disease in CD patients [144].

**Social medical conditions (reimbursement)**

According to national legislation, CD patients may apply for reimbursement to cover the additional costs associated with a GFD. The amount to be refunded from the local municipality is calculated for the individual patient, which is based on individual factors including gender and age.
Non-celiac gluten sensitivity
In recent years, conditions that may not be classified as CD or classical (IgE-mediated) wheat allergies but that are associated with a variety of symptoms that follow the ingestion of gluten-containing products, have been described. In certain patient subgroups where CD is excluded, gluten containing food may trigger gastrointestinal symptoms and fatigue, which in turn diminishes upon initiation of a GFD. The existence of non-celiac gluten sensitivity as a nosological entity is controversial, and the mechanisms are under investigation. Relationships with, for example, other food proteins and carbohydrate intolerance are not clarified [145].

Table 2. Clinical recommendations with evidence level (EL) and recommendation grade (RG).

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<thead>
<tr>
<th>Clinical recommendation</th>
<th>EL</th>
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<tr>
<td>Patients with symptoms or clinical findings consistent with classical CD should be screened for CD</td>
<td>1b</td>
<td>A</td>
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<td>First-degree relatives of CD patients should be screened for CD</td>
<td>2b</td>
<td>B</td>
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<tr>
<td>Patients with dermatitis herpetiformis should be screened for CD</td>
<td>2b</td>
<td>B</td>
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<tr>
<td>Patients with unexplained iron-deficiency anaemia should be screened for CD</td>
<td>1b</td>
<td>A</td>
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<tr>
<td>≥ 4 biopsies from the duodenum and ≥ 1 biopsy from the duodenal bulb should be obtained</td>
<td>1b</td>
<td>A</td>
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<tr>
<td>The combination of IgA anti-TG2 and IgG anti-DGP ensures high sensitivity and specificity in patients with and without IgA deficiency</td>
<td>1b</td>
<td>A</td>
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<tr>
<td>The absence of HLA-DQ2 and HLA-DQ8 excludes CD (negative predictive value close to 100%)</td>
<td>2b</td>
<td>B</td>
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<td>HLA typing can be used to exclude CD in patients with discrepancy between serology and histology or in patients having ingested a GFD prior to diagnostic assessment</td>
<td>3b</td>
<td>B</td>
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<td>Capsule endoscopy can be used as an alternative diagnostic modality in patients with clinical and serological suspicion of CD where upper endoscopy cannot be performed</td>
<td>1a</td>
<td>A</td>
</tr>
<tr>
<td>In patients on a GFD, negative serology and normal histology cannot be reliably used to exclude CD</td>
<td>2b</td>
<td>B</td>
</tr>
<tr>
<td>The treatment for CD is a lifelong GFD</td>
<td>1b</td>
<td>A</td>
</tr>
<tr>
<td>All of the patients with confirmed CD should be offered dietary guidance by a clinical dietician</td>
<td>5</td>
<td>D</td>
</tr>
<tr>
<td>The plasma vitamin and mineral levels should be measured and substituted</td>
<td>2b</td>
<td>B</td>
</tr>
<tr>
<td>Assessment of the GFD should be monitored based on history and IgA anti-TG2 measurements</td>
<td>2a</td>
<td>B</td>
</tr>
<tr>
<td>Follow-up of CD patients should include biochemical assessment of vitamin and mineral deficiencies</td>
<td>4</td>
<td>C</td>
</tr>
<tr>
<td>Patients with classical CD should have their bone mineral density measured with a DXA scan at diagnosis</td>
<td>2b</td>
<td>B</td>
</tr>
<tr>
<td>Treatment of decreased bone density in CD is primarily a GFD</td>
<td>2b</td>
<td>B</td>
</tr>
<tr>
<td>Patients with suspected refractory CD should undergo repeat duodenal biopsies with histological assessments</td>
<td>1b</td>
<td>A</td>
</tr>
</tbody>
</table>

Table 3. Modified Marsh (Oberhuber) classification of histological changes in duodenal biopsies in celiac disease [3].

<table>
<thead>
<tr>
<th>Modified Marsh (Oberhuber)</th>
<th>Increased intraepithelial lymphocytes</th>
<th>Crypt hyperplasia</th>
<th>Villous atrophy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 0</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Type 1</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Type 2</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Type 3a</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes (partial)</td>
</tr>
<tr>
<td>Type 3b</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes (subtotal)</td>
</tr>
<tr>
<td>Type 3c</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes (total)</td>
</tr>
</tbody>
</table>

SUMMARY
This national clinical guideline approved by the Danish Society for Gastroenterology and Hepatology describes the diagnosis and treatment of celiac disease (CD) in adults. CD is a chronic immune-mediated enteropathy of the small intestine triggered by the ingestion of gluten-containing proteins, which are found in wheat, rye, and barley. The disease prevalence is 0.5-1.0%, but CD remains under-diagnosed. The diagnosis relies on the demonstration of lymphocyte infiltration, crypt hyperplasia, and villous atrophy in duodenal biopsies. Serology, malabsorption, biochemical markers, and identification of specific HLA haplotypes may contribute to CD diagnosis. Classical CD presents with diarrhoea and weight loss, but non-classical CD with vague or extraintestinal symptoms is common. The treatment for CD is a lifelong gluten-free diet (GFD), which, in the majority of patients, normalises the small intestinal mucosa and absorption. Adherence to a GFD usually requires dietary advice from a clinical dietician. The monitoring of antibody levels and malabsorption markers is crucial during follow-up and allows for early treatment of disease complications. Important complications include osteoporosis, iron and vitamin deficiencies, and enteropathy-associated T-cell lymphoma.

LITTEURATURE


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