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Coeliac disease in the spotlight

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Coeliac disease in the spotlight

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1 Introduction

Coeliac disease affects more than 1% of the population and it is therefore very likely that every physician, regardless of his/her specialisation, will frequently face a patient with this condition. For this reason, it is very important to know the principles of management of the disease including its pathophysiology, epidemiology, clinical presentation, diagnostic procedures, treatment and long-term management options.

The information presented by the authors of this study material, together with case studies provides the most recent knowledge about coeliac disease required to optimise the quality of care for these patients, which is still often sub-optimal.

We sincerely hope that you will enjoy reading this study material and that it will serve you as a useful reference in your future practice.

Editorial Board.

2 History of coeliac disease

OBJECTIVES:

- To learn about the history of the development of coeliac disease.
- To learn about the trend in the development of diagnostic methods for coeliac disease.

Ancient history

A long, long time ago, there was no coeliac disease on planet Earth. This was not the result of poor awareness and poor diagnostic possibilities or the fact that humans had different genes. This was a result of the fact that, at that time, there was no gluten in their diet.

Man was a hunter and a gatherer, eating fruits, nuts, tubers and occasionally the meat of hunted animals. This diet lasted for a very long time, from the beginning of humankind (approx. 2.5 million years ago) and remained unchanged until 10,000 years ago. It was only after the end of the last Ice Age, with the onset of major climate changes, that men started to grow food. The agricultural revolution in the Neolithic period thus forever changed the way people live. In South-East Asia between today's southern Turkey and Iraq, people began to cultivate wild cereals at the end of the Ice Age. These first types of wheat, barley and rye did not contain much gluten. It is known that the cultivation of cereals relates to the spread of agricultural populations across the Mediterranean and the Pannonian plain into Europe. As the population grew, so did the need for food and increased food production. As a result, new types of cereals appeared, which enabled a larger yield of crops with higher content of gluten and other proteins in the grain. Bread gradually became a basic everyday food. In the 16th century, the production of pasta and other flour products spread from southern Italy throughout Europe. The gluten content in the daily diet of the European population has only increased significantly in the last three centuries. A significant percentage of the population never developed a tolerance to this new protein, gluten, and coeliac disease developed.

History

Clinical symptoms of malabsorption were described from around the 6th century BC in India. In ancient Greece, in the 1st century BC, the physician Areteus from Cappadocia clearly described the clinical picture of the disease (the classic, gastrointestinal form) naming it *koiliakos*. The adjective "coeliac" is the Latin version of the Greek word "koilia", which means abdomen. Subsequent descriptions of the disease can be traced back to the 17th and 18th centuries. Dr Mathew Baillie, unaware of Areteus, described chronic diarrhoea in adults characterised by a large, distended abdomen, for which he advised a diet (rice), but his publication went unnoticed. In 1888, an English physician, Dr Samuel Gee, a leading paediatrician of that time, published a description of the clinical picture of coeliac disease in London, and his publication became the basis of the modern description of the disease. Gee, like Baillie, believed that "If a patient is cured at all, it must be by the means of a diet." In 1908, the American paediatrician Herter published a book on coeliac disease, which is why the disease was later often called Gee-Herter's disease. His greatest contribution was the finding that children with coeliac disease could tolerate fats better than carbohydrates. In 1920, Sidney Haas introduced a very successful banana diet in the treatment of children with coeliac disease. His publication was a great success, and for several decades, the "banana diet" was very popular. The diet completely excluded bread and grains and was, in principle, a form of a gluten-free diet. However, it was only after World War II in 1950, that a Dutch paediatrician, W. K. Dicke, made a fundamental discovery by observing that the causative factor for the disease was a protein called gluten from the wheat grain. In his doctoral dissertation, he demonstrated a dramatic improvement in clinical symptoms of the disease when wheat, rye and oats were excluded from the diet. He later discovered that the toxic component in wheat flour was alcohol-soluble gliadin. At the time of Dicke's discovery, other research enabled the identification of the pathological substrate of coeliac disease. Post-mortem reports of patients with tropical sprue described morphological changes in the small intestine, although these were initially believed to be artefacts of autolysis. Paulley was the first researcher to demonstrate with certainty that mucosal changes in the small intestine are characteristic of coeliac disease. This was later confirmed by the introduction of a peroral biopsy of the small intestine. A major breakthrough in the field of diagnostics occurred in the late 1950s when Margot Shiner described a new intestinal biopsy device with which she successfully performed a biopsy of the distal duodenum. This, together with the development of a simple capsule by Crosby, allowed the identification of characteristic changes in the mucosa of the proximal gastrointestinal tract – i.e., mucosal atrophy. In the 1960s, three very important new fundamentals of coeliac disease emerged: the knowledge that gluten is the triggering factor for the disease, knowledge about specific changes in the intestinal mucosa, and the possibility of performing a biopsy of the small intestine with an instrument.

Recent history

The 2nd meeting of the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) in Interlaken in 1969 opened a new chapter in the history of coeliac disease. There, the first criteria for establishing a diagnosis were established: evidence of abnormal morphology of the small intestinal mucosa, its normalisation after the elimination of gluten from the diet, and relapse after intentional gluten exposure – gluten challenge. Based on the characteristic changes in the small intestinal mucosa that occur as a result of gluten consumption, coeliac disease has been called *gluten enteropathy*.

The first criteria of the ESPGHAN for diagnosing coeliac disease in 1970 (the so-called "classic criteria") were therefore based on changes in the intestinal mucosa, which are today most often described according to the Marsh/Oberhuber classification (Chapter 6). In the 1980s, after the discovery of coeliac disease-specific antibodies, the first critical comments on the criteria appeared, hence modified criteria were adopted at the 22nd ESPGHAN meeting in Budapest in 1989. The basic change was to abandon the mandatory gluten challenge, a so-called diagnostic procedure with three biopsies, and the importance of serological tests was emphasised.

Since 1990, coeliac disease has been increasingly described as an autoimmune disease associated with a specific HLA-haplotype DQ2 or DQ8. The missing autoantigen, tissue transglutaminase, was discovered in 1997 in Germany, thus it was unanimously accepted that coeliac disease is an autoimmune condition, the trigger of which is gluten, and that the autoantigen is tissue transglutaminase (Chapter 4). Along with the changes in the understanding of the pathogenesis of coeliac disease, knowledge of the clinical presentation of the disease also changed. The perspective that coeliac disease is a childhood disease of the white population, mostly with a characteristic phenotype (i.e., blue-eyed, and light-haired children), changed in the 1980s. Coeliac disease was also found to be increasingly associated with other diseases (Chapter 7). It has become clear

that the presentation of coeliac disease is changing, with a decreasing number of gastrointestinal symptoms and signs and an increasing number of various extraintestinal complications (Chapter 5). These facts probably contributed to the increasing attention and in-depth research on coeliac disease with significant changes in the epidemiology of the disease (Chapter 3).

Progress and innovations in the field of coeliac disease diagnostics

At first, antigliadin antibodies (AGA) were used in clinical practice, followed by anti-endomysial antibodies (EMA), which were first described in patients with coeliac disease in 1984 and were quickly introduced into routine use. EMA have long been the gold serological standard for diagnosing coeliac disease. Antibodies against tissue transglutaminase (TGA) were introduced at the turn of the millennium. Antibodies against deamidated gliadin peptide are also used for diagnostic purposes, but they have no advantage over TGA and EMA in diagnosing coeliac disease. In 2005, for the first time, the data on a rapid test that enables the detection of antibodies against tissue transglutaminase was published. This method utilises tissue transglutaminase in erythrocytes to detect TGA in a capillary blood sample. Rapid tests can be performed at the patient's bedside, and the results can be read in 5-10 minutes (Chapter 6). The development of genetics also played a key role in the understanding and diagnostics of coeliac disease. Family and twin studies have shown that the disease has an important genetic background. Most studies focused on the correlation with HLA (human leukocyte antigen) alleles encoded on the sixth chromosome (6p21.3). In particular, the discovery of antibodies against transglutaminase, which are autoantibodies in coeliac disease, and the discovery of a genetic predisposition characteristic of coeliac disease, provided insight into the basic pathogenetic mechanisms that lead to the development of the disease. Today, we know that coeliac disease is not only a disease of childhood and that it not only presents with gastrointestinal complaints. Recent data even show that the frequency of coeliac disease in the elderly is higher than in children.

Due to the active approach to patient-finding, there was a constant increase in the frequency of the disease in Europe and the USA at the end of the last century. Today, coeliac disease is one of the most common chronic diseases (Chapter 3).

At the present time

The ESPGHAN diagnostic criteria published in 2012 brought an important change in the approach to patients with coeliac disease. When establishing a diagnosis, the determination of specific coeliac disease antibodies is most important, and for the first time, the possibility of establishing a diagnosis without intestinal biopsy under certain specific conditions was introduced. The latest 2020 guidelines for diagnosing coeliac disease in children and adolescents further reinforce the no-biopsy approach and eliminate the need for genetic testing in the diagnostic process (Chapter 6).

Although the development of medicine dictates changing the diagnostic criteria based on the evidence and although, in the case of coeliac disease, we no longer talk about gluten enteropathy but rather about a systemic immune disease caused by gluten, one fact remains unchanged in the story. With the unprecedented development that we have witnessed in the field of diagnosis and understanding of coeliac disease, it is quite unusual that there has not been anything new in the treatment of coeliac disease for more than 70 years. A strict lifelong gluten-free diet is still considered the only acceptable treatment. Perhaps it is here where there is more room for future research and progress, which is already underway (Chapter 8).

QUIZ

1. Why was there no coeliac disease in the distant past?
2. What discovery led to the first major breakthrough in diagnosing coeliac disease?

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3 Epidemiology

OBJECTIVES:

- To learn about the incidence and prevalence of coeliac disease.
- To learn about the trends in diagnosed coeliac disease across Europe.
- To learn about the prevalence of undiagnosed coeliac disease.

REMEMBER:
Incidence is the number of newly diagnosed cases per unit of population during a stated period of time.

Prevalence is the total number of cases of a disease existing in a population divided by the total population.

With a prevalence of 1% in the general population, coeliac disease (CD) is one of the most prevalent immune-mediated gastrointestinal disorders. However, many studies and several systematic reviews on the incidence* and prevalence** of CD have shown large variations not only across different regions but also within the same countries. This is partly due to different study methodologies, but it also reflects disparities in the awareness of CD, and variations in healthcare resources and diagnostic protocols used to detect CD.

Incidence and trends in diagnosed coeliac disease

The highest incidence of diagnosed CD in children in Europe has been reported in Norway, Sweden, Finland, and Spain, with rates of more than 50 per 100,000 person-years in children. The lowest incidence has been reported in Estonia (3.1 per 100,000), and Switzerland (5 per 100,000).

Meta-analyses have shown that the pooled incidence of paediatric CD (after the year 2000) was 21.3 per 100,000 person-years compared with 12.9 in adults, with a pooled child-to-adult incidence rate ratio of 1.7.

As shown across Europe, the median age at diagnosis in children has risen sharply: from the study periods before 1990 when the median age at diagnosis was 1.9 years, in the 1990s, when the median age increased to 3.1 years, and then to 7.6 years for study periods since 2000 ($p<0.001$). This is reflected in the higher increase in incidence in the older paediatric age groups than in infants and children younger than 5 years. This is, at least partly, related to greater awareness, better recognition and more active case-finding strategies, thus milder, non-classical and extraintestinal forms of coeliac disease as well as asymptomatic cases are being diagnosed. At the same time, the whole process from a suspected diagnosis of coeliac disease through the diagnostic procedure has been facilitated by the introduction of non-invasive and accurate serological testing, especially EMA after 1990 and TGA after 2000.

Over time, there have been widespread increases in the reported incidence of diagnosed coeliac disease (Scotland 27.7% average annual increase, Norway 23.3%, Sweden 17.9%, Spain 13.3%), with two exceptions (Wales and England). In Sweden, a sharp increase in the incidence of paediatric coeliac disease (the so-called "Swedish epidemic") was observed until the mid-1990s. The incidence rose to a peak of almost 100 per 100,000 person-years in children aged under 5 years and almost 200 per 100,000 in infants. This increase was linked to the introduction of large amounts of gluten into infants' diets soon after the cessation of breastfeeding, as well as to improvements over time in case detection. However, after this "epidemic," childhood-onset coeliac disease stabilised in Sweden in the period from 2003 to 2009. Other regions also reported stabilisation or even a decrease in incidence. In Finland, the adult incidence decreased by 3.4% annually from 2005 to 2014 and the childhood incidence stabilised from 2008 to 2013. As these regions represent areas with some of the highest incidences of coeliac disease, coeliac disease may have reached its peak incidence in these nations. However, it should be noted that due to the lack of national registries, data on the incidence of paediatric coeliac disease at a national level are not available for the majority of countries (in Europe less than 25% of countries have provided data on a national level).

Prevalence of undiagnosed coeliac disease from screening surveys

While in the past CD was considered a rare condition, more recent studies have shown that it is one of the most common life-long disorders.

Screening studies worldwide have revealed that the prevalence of CD is much higher than the reported incidence of diagnosed patients, implying that despite greater awareness, a substantial proportion of individuals with coeliac disease remain undiagnosed. According to cross-sectional screening studies, up to 80 to 90% of CD cases are not recognised. There are several reasons for this: some patients are minimally symptomatic or asymptomatic, and others may have longstanding symptoms attributed to some other diagnoses (such as irritable bowel syndrome) without being tested for coeliac disease.

The prevalence of undiagnosed coeliac disease identified from paediatric screening surveys in Europe ranged from 0.10% across Northern Ireland to 3.03% in Spain.

As shown by meta-analysis, the prevalence of paediatric coeliac disease is significantly higher in Northern Europe (1.82%; 95% CI=1.70-1.95) than in other European regions, Eastern (0.98%; 0.69-1.35), Southern (0.69%; 0.62-0.77) and Western (0.60%; 0.43-0.81). For individual countries since 2000, the prevalence in Sweden (1.93%; 1.80-2.07) has been found in multiple studies to be significantly higher than in all other countries, followed by Spain (1.15%; 0.95-1.38), Italy (0.84%; 0.72-0.97) and Turkey (0.49%; 0.40-0.59). These high rates may reflect greater awareness and better-developed case detection strategies, but they also indicate genuinely high rates of coeliac disease.

Other recent meta-analyses have estimated the prevalence of coeliac disease to be 0.7% in the United States, 0.6% in Asia, 0.5% in Africa, and 0.4% in South America.

The incidence of coeliac disease was reported to be higher in women than men (17.0 vs 7.8 per 100,000 person-years in a pooled analysis), although a meta-analysis of screening studies found only a slight increase in seropositivity among female participants.

Some racial and ethnic differences in the prevalence of coeliac disease have also been reported, independent of differences in testing rates. In the United States, coeliac disease is less common in non-Hispanic black (seroprevalence 0.2%) and Hispanic (0.3%) vs white individuals (1.0%). Likewise, the prevalence of coeliac disease can vary widely between countries despite geographical proximity and even within the same country. It has been shown that 1.4% of individuals in Finland were found by screening to have coeliac disease compared to only 0.6% in the adjacent Russian Karelia, although there are no significant differences in compatible HLA haplotypes. Differences have been found even within the same countries, for example in India, although, the prevalence did not vary by urban vs rural areas or with socioeconomic status. The reasons

for these regional and ethnic differences are unknown, but it is assumed that more than one factor is involved. When comparing different screening studies, it should also be kept in mind that studies may vary in methodology, including the study period, in the age groups of subjects studied, diagnostic tests used and their sensitivity and specificity, in the way the final diagnosis is made, and the proportion of suspected cases confirmed by biopsy.

KEEP IN MIND

- Coeliac disease is one of the most prevalent immune-mediated gastrointestinal disorders.
- Both the incidence and prevalence of coeliac disease in the paediatric population have risen across Europe.
- The prevalence of previously undiagnosed coeliac disease from screening surveys ranges from 0.10% to 3.03% (median = 0.70%).

QUIZ

1. How prevalent is coeliac disease in the general population in Europe?
2. What might be the cause of the differences in the prevalence of coeliac disease in different regions?

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4 Aetiology

OBJECTIVES:

- To understand the pathogenesis of coeliac disease.
- To learn about gluten and its role in the development of coeliac disease.
- To understand the role of genetics in the development of coeliac disease.
- To identify possible environmental factors involved in the development of coeliac disease.

Coeliac disease is a lifelong systemic autoimmune disorder elicited by gluten and related prolamins in genetically susceptible individuals, but various environmental factors also influence the development of the disease.

Pathogenesis of coeliac disease

Both the innate and acquired immune systems are involved in the pathogenesis of CD. After ingesting gluten, digested peptides in the small intestine pass to the lamina propria where they are deamidated and recognised by antigen-presenting cells via their class II HLA (human leucocyte antigen) molecules, triggering an abnormal CD4+ T-cell immune response. The formation of a peptide-HLA molecule complex on the surface of the antigen-presenting cells is responsible for the transcription, configuration and signalling of the events involved in the development of the disease, thus representing an important step in the pathogenesis of CD.

Gluten

The most important factor in the development of CD is gluten, which accounts for 85-90% of the proteins in wheat grain. Gluten (meaning glue in Latin) is the common name for a protein complex that is composed of two groups of proteins divided according to their solubility. The major group are alcohol-soluble prolamins (wheat - gliadins), and the second is acid-soluble glutelins (wheat - glutenins). The term gluten, therefore, indicates a broad group of prolamins found in wheat. Other prolamins showing similar immunogenic peptides are also found in rye (secalins), barley (hordeins), and other closely related grains. The major prolamins of the more distantly related maize (zeins) seem to have evolved independently and show no harmful effects in CD patients. The same is also true of rice (oryzins). Oats (avenins), in their pure form, are not harmful either, but they are often contaminated with wheat or other cereals. In vitro studies have shown that the immunogenicity of oats depends on the cultivar, making their use in patients with CD questionable.

Studies have shown that different gluten peptides act directly against the intestinal mucosa or trigger an immune response. So far, the highest toxicity has been attributed to α-gliadin, which contains the

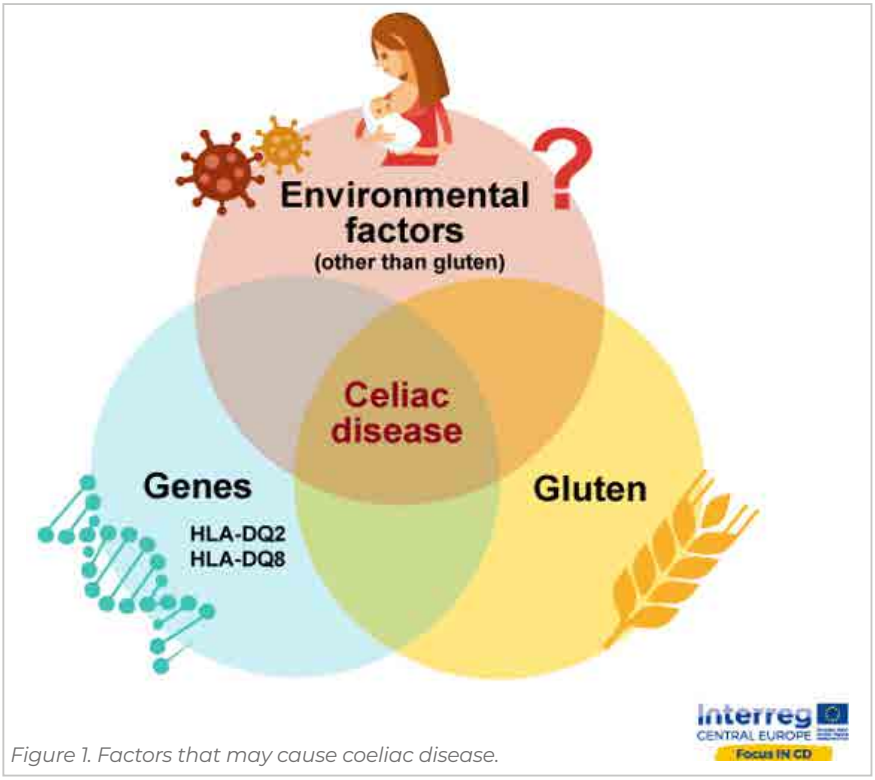

Figure 1. Factors that may cause coeliac disease.

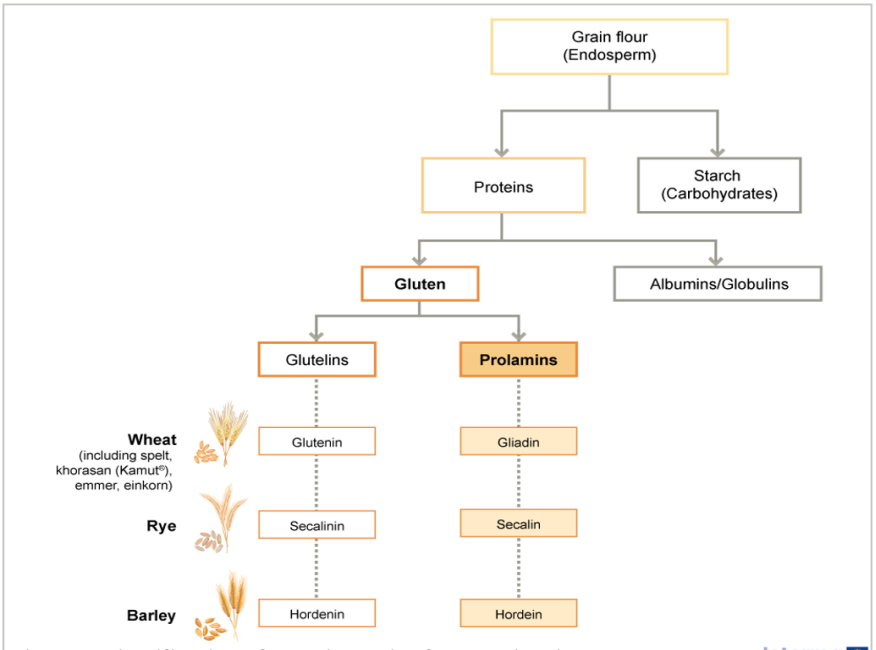

Figure 2. Classification of cereal proteins from grains that are not tolerated in coeliac disease.

most immunogenic peptides.

Gluten is often used in the food and cosmetics industries because of its characteristics, which give viscosity, elasticity, and better structure to the final product. It is especially utilised in bread production giving the bread a greater volume and its typical structure.

Genetic factors

Coeliac disease is a multifactorial disease with a strong genetic background. The most studied association of CD is with the HLA-DQ2 and HLA-DQ8 haplotypes. HLA molecules are members of the major histocompatibility complex, composed of α- and β-chains encoded by specific variants of the HLA-DQA1 and HLA-DQB1 genes. The HLA-DQ2 haplotype is encoded by the DQA1*0501 and DQB1*0201 alleles. It is expressed in about 90% of patients with CD, and the HLA-DQ8 haplotype, encoded by the DQA1*0301 and DQB1*0302 alleles, is expressed in another 5% of patients. Almost all of the other 5% of patients have at least one of the two alleles encoding DQ2 (DQA1*0501 or DQB1*0201).

In the general population, the frequency of genotypes associated with CD is 30-40%, but only about 1-3% of gene carriers develop the disease. A negative test result for DQ2/DQ8 is likely to exclude CD, but a positive result has a lower diagnostic value. In the last decade, genome-wide association studies have found that the HLA locus is the major genetic factor, although at least 39 non-HLA genes have also been associated with an increased risk of developing the disease.

Immunological factors

The primary mechanism involved in the development of CD is an inappropriate immune response to peptides that form gluten, especially prolamins (wheat - gliadin, rye - secalin, barley - hordein). Since these proteins contain large amounts of proline and glutamine, their degradation in the gastrointestinal tract is incomplete. Therefore, some peptides can pass undigested from the intestinal lumen using the transcellular or paracellular pathways. In some individuals, the passage of these gluten peptides across the lamina propria results in the deamidation of gliadin peptide by the enzyme tissue transglutaminase, which increases its immunogenicity and facilitates its binding to HLA-DQ2 and HLA-DQ8 molecules on antigen-presenting cells. Gliadin peptides are then presented to the CD4+ T- cells, which consequently produce large amounts of proinflammatory cytokines, including interferon-gamma, inducing Th1 cells and increasing the formation of tumour necrosis factor-alpha, which plays an important role in intestinal mucosal damage. To a lesser extent, cytokines also induce Th2 cells, which induce clonal expansion of B-lymphocytes and their differentiation into plasma cells, which secrete antigliadin antibodies, anti-endomysial antibodies (EMA) and antibodies against tissue transglutaminase (TGA). Some gliadin peptides that are not recognised by T-lymphocytes activate antigen-presenting cells, intestinal epithelial cells and especially

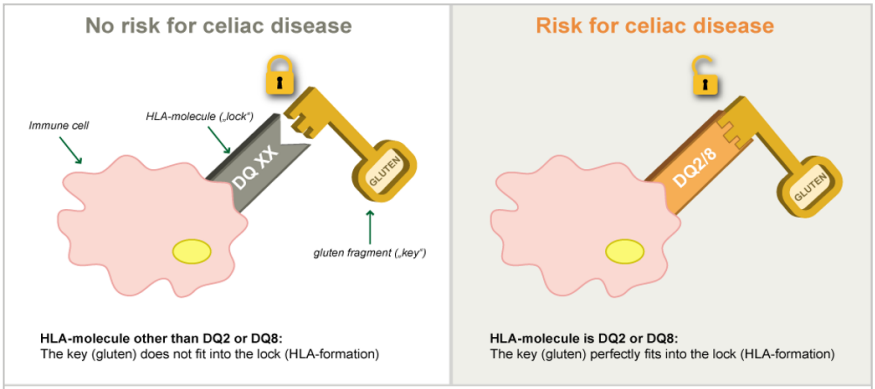

Figure 3. HLA-DQ2/-DQ8 and its role in the development of coeliac disease in the gut.

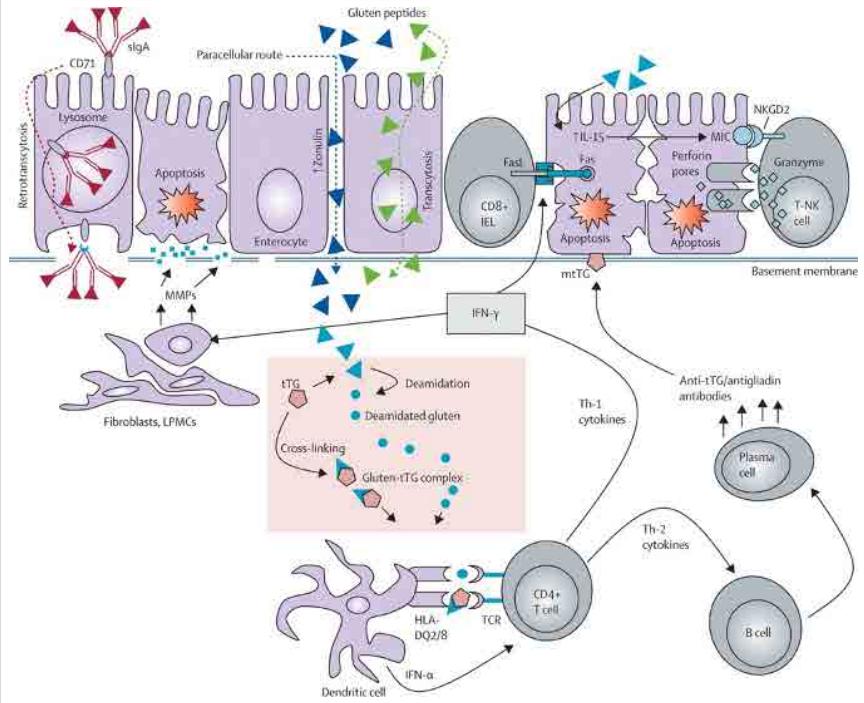

Figure 4. Mechanisms of mucosal damage in coeliac disease (Di Sabatino et al. Lancet. 2009).

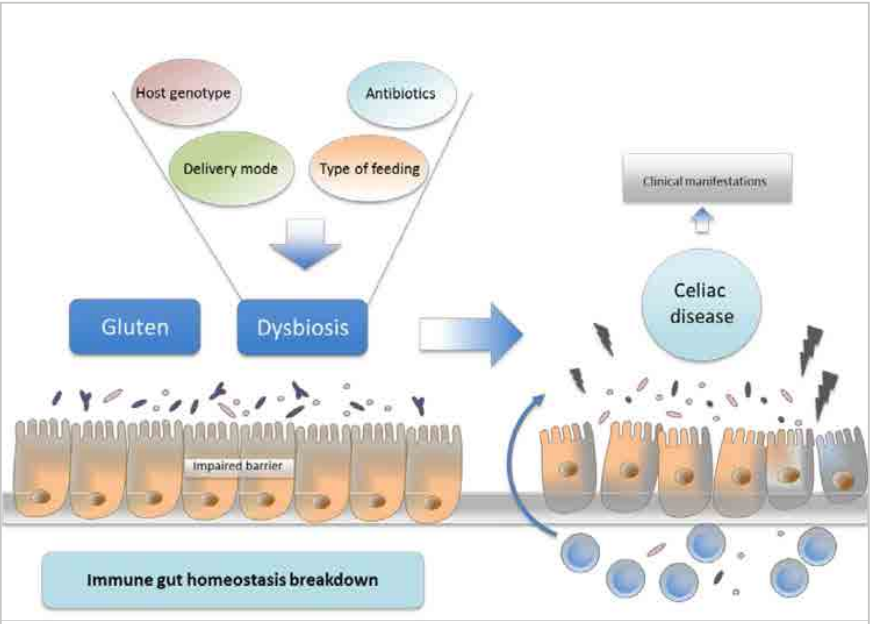

Figure 5. Coeliac disease pathogenesis (Cenit MC et al. Nutrients. 2015).

CD8+ T-lymphocytes. The latter are also stimulated by interleukin-15, leading to an increase in the number of receptors for natural killer cells, thereby promoting cell death and increasing intestinal wall permeability. This inflammatory response results in matrix degradation, mucosal remodelling, intestinal villous atrophy, crypt hyperplasia, and an increased number of intraepithelial lymphocytes.

Environmental factors

Although the HLA genotype and gluten consumption are common in the general population, only a small proportion of genetically susceptible individuals develop CD. This suggests that additional environmental factors play a role in the development of the disease. The effects of the type of delivery, feeding methods after delivery, the use of antibiotics together with the influence of early infections and the gut microbiota, have been studied.

Environmental factor	Association with CD
Type of delivery	None
Feeding methods, amount and timing of gluten introduction.	Neither the time of gluten introduction nor the duration of breastfeeding affects the overall risk of developing the disease.
	Recommendation: The introduction of gluten into an infant's diet anytime from 4 to 12 months of age.
	In children at increased risk of developing CD, early introduction of gluten is associated with an earlier onset of CD, but the cumulative incidence in later childhood is similar in both groups.
	Recommendation: Large amounts of gluten should be avoided in the first weeks after gluten introduction and in early childhood.
Use of antibiotics or other drugs	The use of antibiotics in pregnancy was not associated with the development of CD in the offspring.
	The use of proton pump inhibitors was associated with an increased risk of developing CD, probably due to changes in the gastrointestinal microbiome.
Early infections	Gastrointestinal infections, rotavirus in children, *Campylobacter* infections in adults, and reovirus infections have been suggested as risk factors for developing CD, and rotavirus vaccination has been shown to have a protective effect.
	An increased total number of infections (> 10 vs <4 in the first 18 months of life) was indicative of an increased risk of CD.
	Colonisation with *Helicobacter pylori* may reduce the risk of CD.
	A higher number of respiratory infections in the first 18 months suggested an increased risk of developing the disease later in childhood.
Gut microbiota	Patients with CD have an altered gut microbiota that does not completely normalise even after the introduction of a gluten-free diet.
	The *Bifidobacterium bifidum* concentration was found to be significantly higher in untreated patients with CD than in healthy individuals.
	In children with CD, a higher incidence of duodenal Gram-negative and potentially pro-inflammatory bacteria was found at confirmation of the diagnosis compared to healthy controls.

QUIZ

1. Which of the following best describes coeliac disease?
   a) Coeliac disease is an autoimmune disease that affects only the small intestine.
   b) Coeliac disease is a systemic immune-mediated disease that affects genetically predisposed people.
   c) Coeliac disease is an allergic disease that affects mostly people from atopic families.
   d) Coeliac disease is a food intolerance restricted to wheat and wheat-containing products affecting the small intestine.
   e) Coeliac disease is an enzyme deficiency disorder affecting the breakdown of wheat and other gluten-containing foods.
2. Which HLA haplotypes are related to coeliac disease?
3. What is the frequency of genotypes associated with CD in the general population?
4. Which statement is correct? (multiple answers possible)
   a) Gluten is a protein that comprises a minor part of the wheat grain.
   b) Avenins are noxious for CD patients.
   c) TGA antibodies are secreted due to Th2 stimulation by cytokines.
   d) Gut microbiota might have a role in the development of CD.
   e) Early introduction of gluten is associated with earlier development of CD in at-risk children.

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5 Clinical presentation

OBJECTIVES:

- To understand the diverse clinical presentation of coeliac disease.
- To recognise symptoms and signs that could be associated with coeliac disease.
- To differentiate between different forms of coeliac disease.

The symptoms of CD can be attributed to a combination of inflammation, nutrient deficiency caused by malabsorption, and the autoimmune response to the enzyme tissue transglutaminase. In the past, CD was known as an illness of childhood, with a characteristic clinical presentation of diarrhoea with malabsorption syndrome. Nowadays, we know that CD is a systemic disease that can occur at any age. Although it causes impairment of intestinal absorption, gastrointestinal symptoms occur in only about half of the patients since the disease is not limited to the digestive tract but can manifest itself by many intestinal as well as extraintestinal symptoms and signs or it can even be asymptomatic. Extraintestinal manifestations of the disease can affect almost every organ, including the nervous system, liver, skin, reproductive system, cardiovascular system, and musculoskeletal system, and are usually associated with a more serious clinical and histological picture. Some of these manifestations can present in early childhood, whereas others do not appear until adulthood or advanced age.

It has been shown that the clinical presentation can vary according to the patient's age. In very young children (<3 years), the signs and symptoms of malabsorption are more common than in older children and adolescents, in whom the most common symptom is abdominal pain. In adults, the disease often does not present with characteristic signs and symptoms, but with extraintestinal manifestations or serious complications of the disease, which can, in rare cases, also be seen in childhood. There are vulnerable periods of life when high nutrient demands may lead to severe symptoms faster or more often. These are early childhood (1-4 years of age) and puberty, both characterised by a rapid growth spurt, and the lactation period after giving birth in women.

OSLO Classification of coeliac disease	
Classical CD	Symptoms and signs of malabsorption: diarrhoea, steatorrhoea, bloating, growth retardation or weight loss, anaemia, neurological disorders due to vitamin B deficiency, osteopenia due to vitamin D and calcium deficiency.
Symptomatic CD	Intestinal symptoms without signs of malabsorption: recurrent abdominal pain, vomiting, constipation. Extraintestinal symptoms: fatigue, poor concentration, headaches, migraine, ataxia, dental enamel defects, infertility.
Subclinical CD	No clinical symptoms, only abnormal laboratory levels of certain parameters such as elevated liver transaminases or iron deficiency.
Asymptomatic CD	CD-specific laboratory changes in patients who appear to be symptom-free.
Refractory CD	Despite a long (>12 months) gluten-free diet, the symptoms and signs of malabsorption and villous atrophy persist. The disease is resistant to treatment. While refractory CD has not been reported in children and adolescents with CD, probably around 1% of adult patients are affected, most of whom are over 50 years of age. The following symptoms in a patient with CD keeping a strict gluten-free diet warrant extensive diagnostic work-up: chronic diarrhoea, unintended weight loss, fever, fatigue, and night sweats for unclear reasons. Based on the number and characteristics of certain immune cells (intraepithelial lymphocytes, IEL) in the mucosa, refractory CD is subdivided into type I (RCD1): Marsh 3 lesions with normal types of intraepithelial lymphocytes and type II (RCD2): Marsh 3 lesions with an increased number (>20%) of aberrant intraepithelial lymphocytes (CD3 and CD8 negative) with pre-malignant characteristics and T-cell receptor clonality. Patients with RCD should be diagnosed, treated, and monitored in specialist units. If the diagnosis is confirmed, medical therapy (in addition to a gluten-free diet) and close monitoring are needed due to the increased risk of malignancy in the small intestine (enteropathy-associated T-cell lymphoma, EATL) in patients with type II RCD.
Potential CD	The symptoms are non-specific or absent, CD-specific antibodies are positive and the duodenal mucosa appears normal (Marsh 0 or 1).

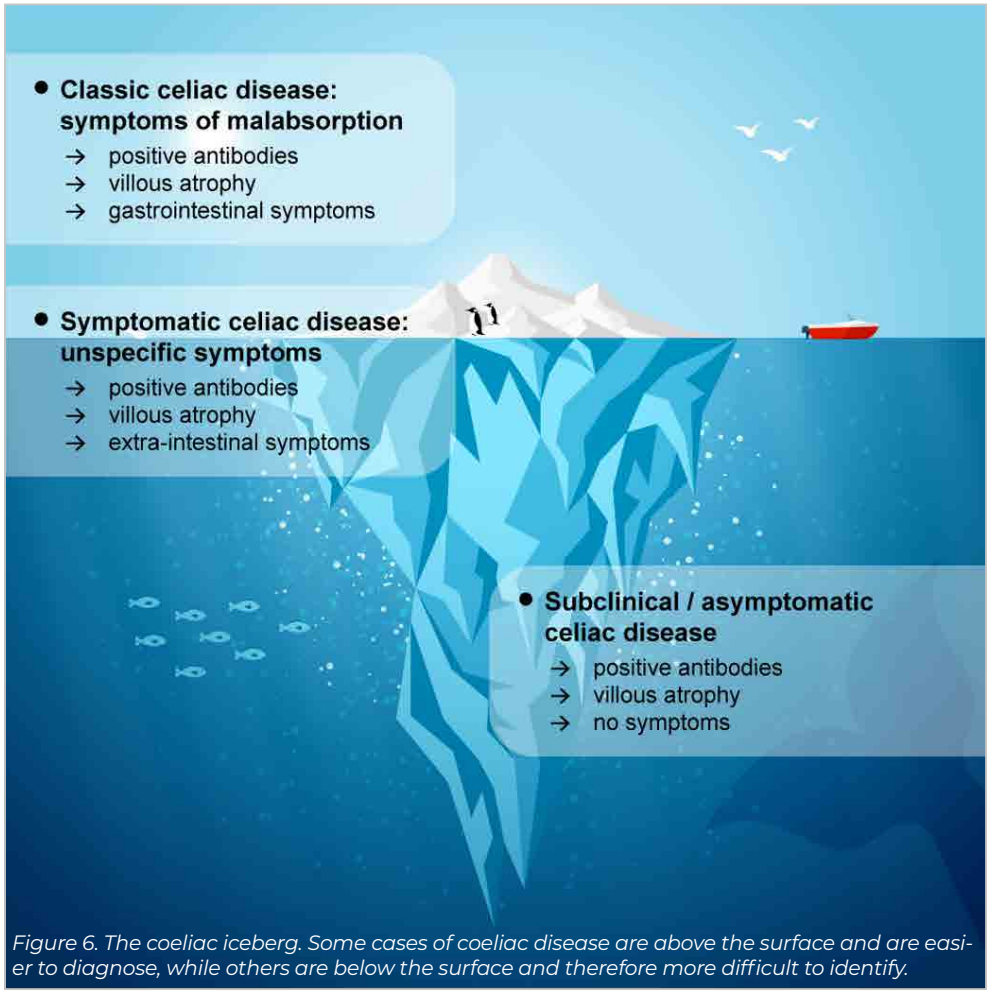

Figure 6. The coeliac iceberg. Some cases of coeliac disease are above the surface and are easier to diagnose, while others are below the surface and therefore more difficult to identify.

Gastrointestinal symptoms and signs	Diarrhoea, fatty, pale, foul-smelling stools or an increase in the stool volume, bloating, flatulence, lactose and other carbohydrate intolerances, abdominal pain, recurrent vomiting, constipation. **Mouth and teeth:** mouth ulcers, dental enamel defects.
Liver, spleen, and pancreatic disorders	Elevated levels of liver enzymes, autoimmune hepatitis, autoimmune biliary disease, severe liver failure, spleen function disorder (hyposplenism), pancreatic insufficiency.
Haematological and bleeding disorders	Anaemia (iron deficiency, folate deficiency, vitamin B12 deficiency), bruising or prolonged bleeding time (vitamin K deficiency), malignant disorders of immune cells (lymphoma).
Growth, development, and general health	Low body weight or slow weight gain, weight loss, fatigue, general weakness, lack of concentration, growth retardation, delayed puberty, moodiness.
Skin disorders	Dermatitis herpetiformis (Duhring's disease): a cutaneous manifestation of CD, characterised by itching and a blistering rash typically localised on the elbows, knees, shoulders, back, and buttocks or other extensor surfaces, with extremities symmetrically affected. Gastrointestinal symptoms are rare. Skin biopsy shows the pathognomonic granular deposits of immunoglobulin A in the papillary dermis. Damage to the intestinal mucosa can also be found. Patients with severe skin symptoms may need special medications in addition to a gluten-free diet.
Cardiovascular disorders	Dilatative heart disease, heart failure.
Pulmonary disorders	Restrictive pulmonary disease (pneumonitis or alveolitis), frequent airway infections.
Kidney disorders	Proteinuria, haematuria.
Musculoskeletal system	Swollen legs, muscular cramps, or pain (myalgia), muscular weakness and decreased muscular tone, joint pain and inflammation, osteoporosis and osteopenia, rickets.
Neurological problems	Headache, mood and behavioural disorders, hyperactivity, concentration problems, tiredness, foggy mind, depression, sensory or gait problems, ataxia, epilepsy.
Reproductive system	Infertility and miscarriages, lower birth weight of children.
Nutrient deficiencies	Calcium, vitamin D, vitamin B12, iron.
Coeliac crisis	a) acute abdomen with intense pain, distension, and poor general condition. b) severe disbalance of body fluids as a consequence of intense diarrhoea, loss of potassium, sodium, chloride, calcium, and other minerals causing general weakness and cardiac problems.

SYMPTOMS

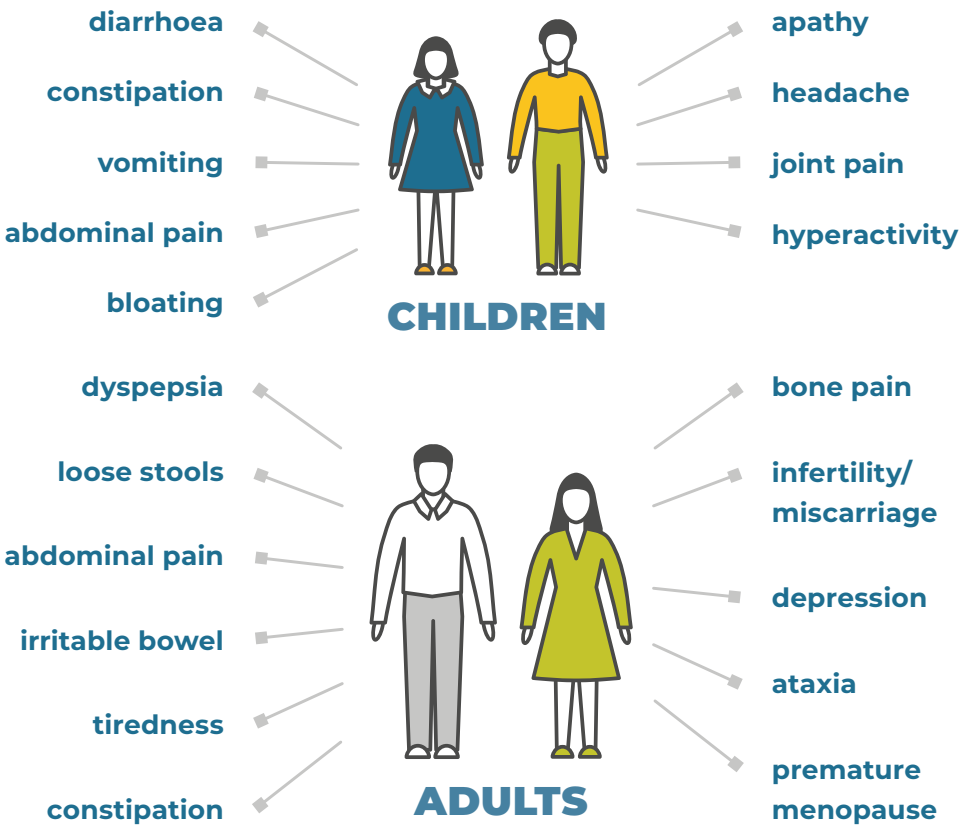

Figure 7. Possible symptoms of coeliac disease.

SIGNS

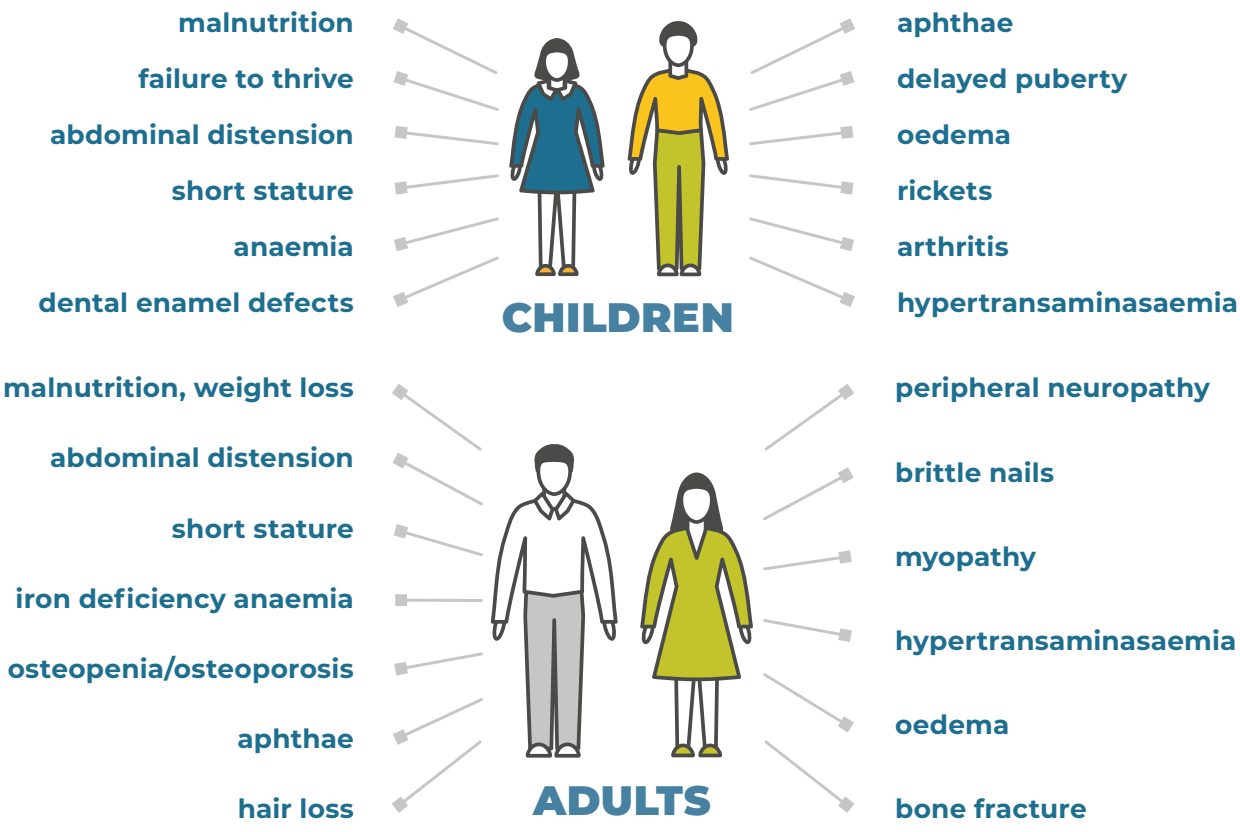

Figure 8. Possible signs of coeliac disease.

CASE STUDIES

A 15-year-old boy was referred to the outpatient clinic because of microcytic anaemia. His mother explained that the boy had been treated unsuccessfully for anaemia with iron supplements for more than two years. He has had frequent migraine attacks, occasional mild abdominal discomfort and has been very tired most of the time. He defecates twice a day, and the stool is of normal colour and consistency. From time to time, he has had mouth ulcers but currently has none. On physical examination, he was slightly pale, with no other obvious abnormalities. Serological tests for coeliac disease were highly positive.

A 16-year-old girl was referred to the outpatient clinic because of suspected lactose intolerance. She explained that she has been avoiding milk for the last 6 years, since she felt nauseous after drinking it or eating dairy products, except cheese. She observed similar problems when eating croissants. In the past few years, she noticed that when eating pizza, she felt early satiety and could only tolerate one piece. She has had no abdominal pain and her defecation and appetite were also normal. She had been treated for microcytic anaemia with iron supplements for a year. Her haemoglobin levels were normal at the last check-up. Serology for coeliac disease was highly positive.

An 8-year-old girl was referred to the outpatient clinic because of abdominal distention and frequent flatulence. Her mother explained that the girl has had a slightly distended abdomen and frequently passed wind since the age of 2 years. From time to time, she has complained of mild abdominal pain, and sometimes her stools were soft and sticky. Her parents had a feeling that her complaints were more frequent if she ate very starchy food. For the last three months, she has had no complaints except frequent wind, which was not related to the type of food she had eaten. Her appetite was good, she defecated once per day, and her stool consistency and colour were normal. Coeliac disease serology was highly positive.

An 18-month-old girl was admitted to hospital because of dehydration due to diarrhoea. The complaints had started 2 weeks previously when she presented with signs of acute gastroenteritis with vomiting and diarrhoea. She stopped vomiting 4 days prior to admission, but she still had liquid stools with mucus but no blood, 6 to 10 times per day. Her appetite was bad, she was tired, pale and apathetic. At home, they had already tried a lactose-free diet, racecadotril and probiotics, but the frequency and form of the stools had not changed. She has had no fever and has not complained of abdominal pain. At admission, she was mildly dehydrated, with a prominent distended abdomen. Laboratory results showed hypoalbuminaemia, with mild electrolyte imbalance, and inflammatory markers were low. Stool cultures were negative. Coeliac disease POCT was immediately positive, and serological markers for CD were very high.

A 72-year-old woman came to the coeliac disease outpatient clinic after many years of searching for the cause of her health problems. At the age of 67, the symptoms that had occasionally occurred in previous years became more pronounced. An extremely uncomfortable feeling in her body, which the patient described as “feeling creepy in my own body”, accompanied by the symptoms of diagnosed gastritis, forced the patient to self-initiate a gastritis diet to eliminate foods that she suspected were causing the feeling of discomfort. As the new diet regimen and drugs prescribed for gastritis did not produce the desired results, and she became very weak and malnourished, the family doctor referred her to a psychiatrist for suspected eating disorders. She was then diagnosed with anxiety disorder and depression, but her complaints continued despite the medication she received. At the last visit to the gastroenterologist, serological tests for CD were ordered and TGA were positive. Gastroscopy with biopsy confirmed damage to the small intestinal villi (Marsh stage 3).

QUIZ

1. Which of the following is/are correct? (multiple answers possible)
   a) Coeliac disease always presents with gastrointestinal symptoms.
   b) Coeliac disease can present with gastrointestinal symptoms.
   c) Coeliac disease never presents with gastrointestinal symptoms.
   d) Coeliac disease can present without gastrointestinal symptoms.
   e) Coeliac disease can be asymptomatic.
2. How does the clinical presentation of CD differ between small children and adults?
3. Which are the vulnerable periods when the clinical presentation of CD can be more severe?
4. What are the characteristics of classical CD?
5. What is the common skin manifestation of CD? How is it diagnosed and treated?
6. In which patients would coeliac disease be among the most likely diagnoses? (multiple answers possible)
   a) A 14-year-old boy with microcytic anaemia.
   b) A 6-year-old boy with fever and haematuria.
   c) A 13-year-old girl with recurrent abdominal pain.
   d) A 3-month-old girl with chronic diarrhoea and abdominal distention.

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6 Diagnostics

OBJECTIVES:

- To understand the diagnostic possibilities for the diagnosis of coeliac disease.
- To understand the importance of a regular diet before testing for coeliac disease.
- To understand the role of POCT tests in diagnosing coeliac disease.
- To be able to explain the requirements of a no-biopsy approach for diagnosing coeliac disease.
- To understand the role of genetic testing in the diagnosis of coeliac disease.
- To learn what tests should be done at the primary-care facility when suspecting coeliac disease.

The diagnosis of CD is guided by the clinical presentation, but the definitive diagnosis is based on the presence of a specific immune response and characteristic histological changes in the small intestinal mucosa.

Blood tests – serological tests

The initial step in diagnosing coeliac disease is the determination of the presence of specific antibodies in the blood. In coeliac disease, it is possible to detect antibodies against the enzyme tissue transglutaminase (TGA), found in many human tissues. These antibodies are produced only when gluten is consumed and are very rarely found in individuals without the disease. They usually fall to normal levels within a couple of months after a patient with coeliac disease starts a strict gluten-free diet. The same is also true for anti-endomysial antibodies (EMA), which are as reliable as TGA, although the test is more difficult to perform and is, therefore, more expensive. Thus, clinicians use it as a second-line test to confirm a previously positive TGA test. The current ESPGHAN (European Society for Paediatric Gastroenterology, Hepatology and Nutrition) guidelines for the diagnosis of coeliac disease in children allow clinicians to diagnose the disease in certain cases without upper endoscopy and intestinal biopsy. This approach can be used in children and adolescents who have very high levels of TGA and a positive confirmatory EMA test in a second blood sample. Since both tests typically determine only the presence of IgA class antibodies, the total immunoglobulin A (total IgA) concentration also needs to be determined. If low total IgA is found, tests determining IgG antibodies should be used.

Point-of-care testing

Point-of-care tests for determining autoantibodies in capillary blood (finger-prick blood) are widely available in many regions. However, these tests are not sufficient to diagnose coeliac disease and the results need to be discussed with a clinician. Exclusion of gluten from the diet based solely on these tests can seriously influence the performance and interpretation of laboratory blood tests that are more reliable and need to be performed to confirm the diagnosis.

Figure 9. Coeliac disease point-of-care test demonstration.

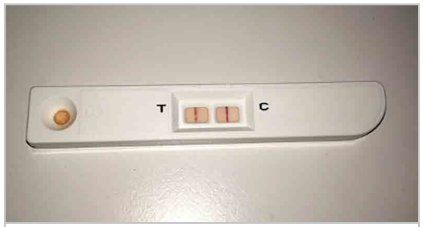


Figure 10. Coeliac disease point-of-care test (positive).

Intestinal biopsy

If the initial autoantibody test is suggestive of coeliac disease, further investigations are always needed to confirm the diagnosis. In some cases, it is necessary to perform an intestinal biopsy. It is recommended that at least one sample is taken from the first part of the duodenum (bulbus) and at least four samples from the distal part of the duodenum.

Figure 11. Endoscope.

Upper endoscopy with biopsies from the duodenum enables the pathologists to determine the changes typical of coeliac disease:

1. Increased number of intraepithelial lymphocytes (IEL) (normal <25 IEL/100 enterocytes).
2. Shortening of the mucosal villi - Villous atrophy (normal villous height to crypt depth ratio is 3:1 to 5:1).
3. Elongation of the crypts - Crypt hyperplasia.

The histopathological findings in CD are commonly classified according to the Marsh-Oberhuber classification, which defines four subtypes of mucosal changes. Type Marsh 0 represents normal intestinal mucosa, Marsh 1 is the infiltration phase with lymphocytes infiltrating the epithelium of the intestinal villi, Marsh 2 is the infiltrative-hyperplastic phase with crypt hypertrophy and hyperplasia, and lymphocytes markedly infiltrating the epithelium. Marsh 3 is the destructive phase, which is the most common finding in patients with CD. There are no villi, the crypts are severely hyperplastic and hypertrophic, and the infiltration of the epithelium with lymphocytes is very pronounced.

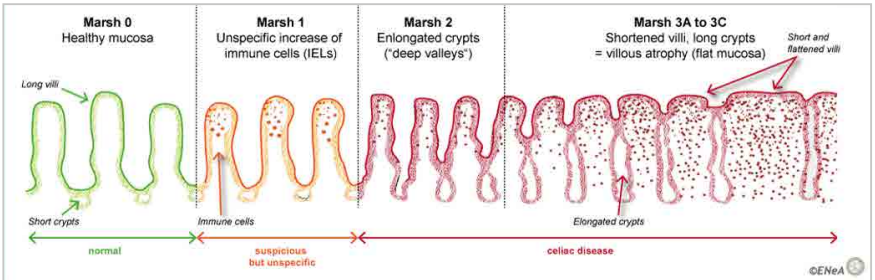


Figure 12. Marsh-Oberhuber classification of mucosal changes in coeliac disease.

The histology report alone indicating coeliac disease without positive autoantibodies is not sufficient to diagnose coeliac disease!

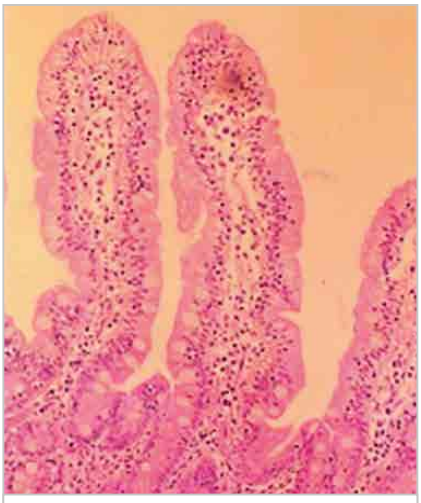


Figure 13. Normal small intestinal mucosa.

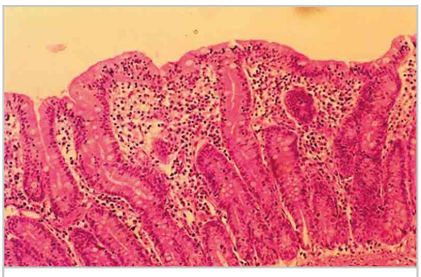


Figure 14. Mucosal changes in coeliac disease - Marsh 3C.

Despite being a gold standard for diagnosing CD, several pitfalls in the interpretation of duodenal biopsies must also be considered. Histological analysis has been reported to lack diagnostic accuracy owing to the high interobserver variability, differences between routine and more specialised pathology laboratories, low rates of the correct orientation of biopsy samples, and the low number of samples taken. These factors can lead to an inadequate interpretation of mucosal changes. Therefore, new methods for the detection of intestinal TGA are being developed to supplement histological findings in diagnosing CD.

Due to greater awareness of CD, there is an increasing number of symptomatic patients with positive CD antibodies despite histologically normal intestinal mucosa and more patients with negative or fluctuating serum antibodies and normal intestinal mucosa. In these two conditions (potential, pre-potential CD), it has been observed that the presence of intestinal TGA is the only mucosal immunological marker of CD. Detection of intestinal TGA can therefore assist in the diagnosis in cases of doubtful histology results.

HLA testing

Genetic testing is especially helpful in excluding coeliac disease. Individuals who are negative for HLA-DQ2 or HLA-DQ8 have no risk of developing the disease and further tests are not necessary. Genetic risk markers specific to the disease, i.e., HLA-DQ2 and HLA-DQ8, can be found in approximately one-third of the general population. According to the ESPGHAN guidelines, genetic testing is not mandatory for confirmation of the diagnosis in children and adolescents.

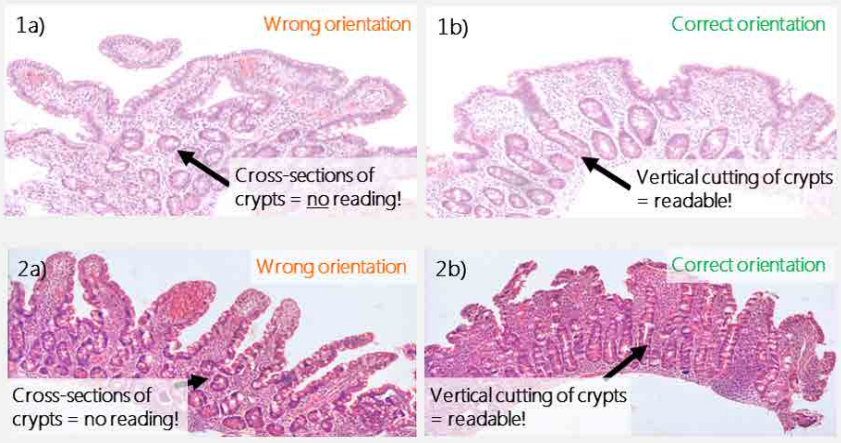


Figure 15. Impact of biopsy orientation. Biopsy 1a and 2a (left side) both show apparently normal villi, but only cross-sections of the crypts are visible, which indicates wrong orientation and cutting, which does not allow any reading. However, pathologists have interpreted 1a and 2a as normal (Marsh 0 to 1). In pictures 1b and 2b (right side), the same biopsies are shown, but they have been tilted and re-cut in the correct orientation (perpendicular cutting). Now it is obvious that both 1b and 2b show villous atrophy and crypt hyperplasia and the same pathologists reported Marsh 3B to 3C for these biopsies. Both biopsies clearly support a diagnosis of CD in combination with positive serology, but misclassification can easily happen if the pathologist does not consider the correct orientation and cutting! Source: FocusIN-CD with histology slides from Taavela et al. 2013.

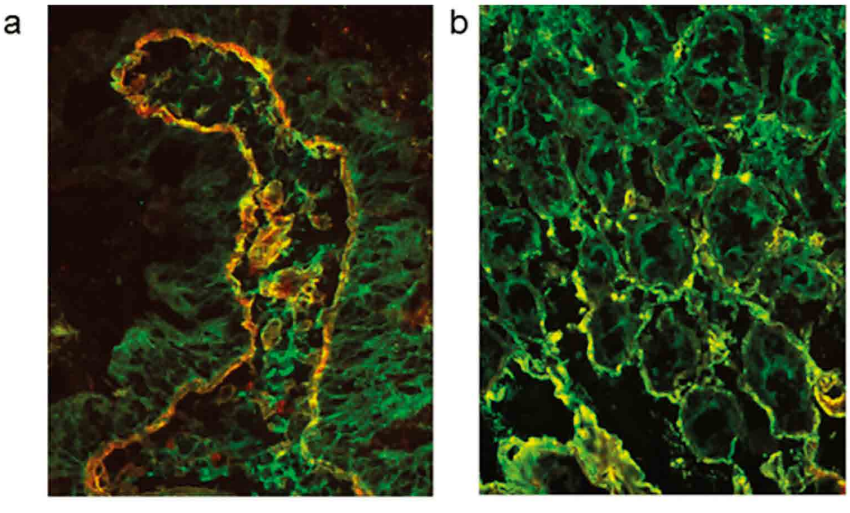


Figure 16. Intestinal TGA deposits detected (red colour - TGA IgA antibodies).

Diagnosing coeliac disease without intestinal biopsy

Based on the current ESPGHAN guidelines, when all specific criteria have been met, the diagnosis of coeliac disease in children and adolescents can safely be made without the need for upper endoscopy and intestinal biopsy.

1. The TGA-IgA levels must be very high, i.e., more than 10 times the upper limit of the cut-off value.
2. Auto-antibodies against EMA must be positive in a second blood sample.
3. A paediatric gastroenterologist should be involved in the process and should explain the no-biopsy approach to parents and patients.

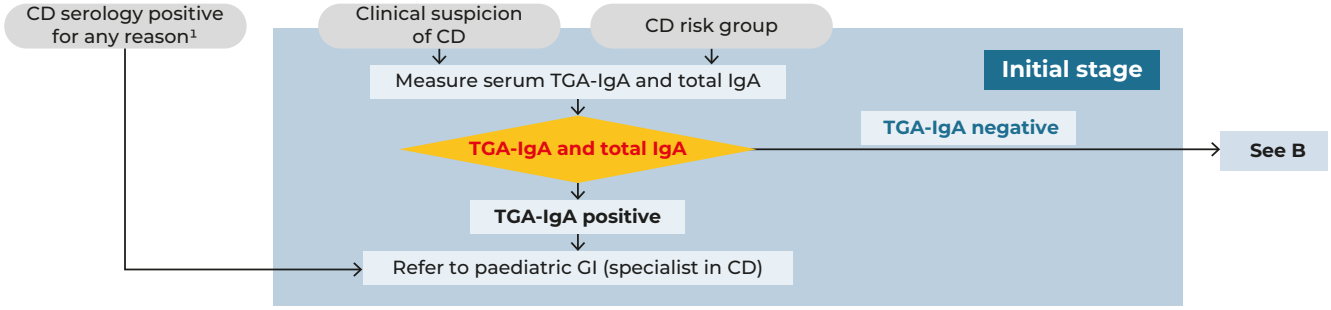
However, according to the current guidelines, upper endoscopy must be performed to confirm the diagnosis of coeliac disease in adults.

WHAT TO DO IN THE PRIMARY CARE FACILITIES WHEN CD IS SUSPECTED:

1. Determine the IgA antibody level:
   a. If IgA is normal, determine IgA TGA;
   b. if IgA is undetectable, perform IgG TGA or if unable, refer to a (paediatric) gastroenterologist;
2.) If IgA TGA is positive – refer to a (paediatric) gastroenterologist.
3.) **Do not advise starting a gluten-free diet!**

ESPGHAN 2020 guidelines for diagnosing coeliac disease in children and adolescents:

A.



B.

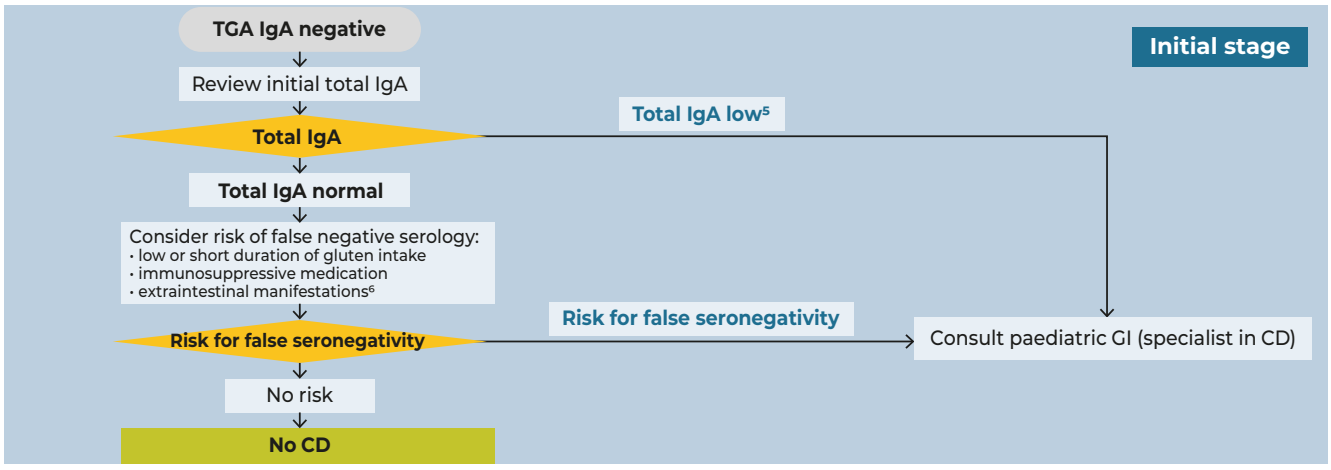
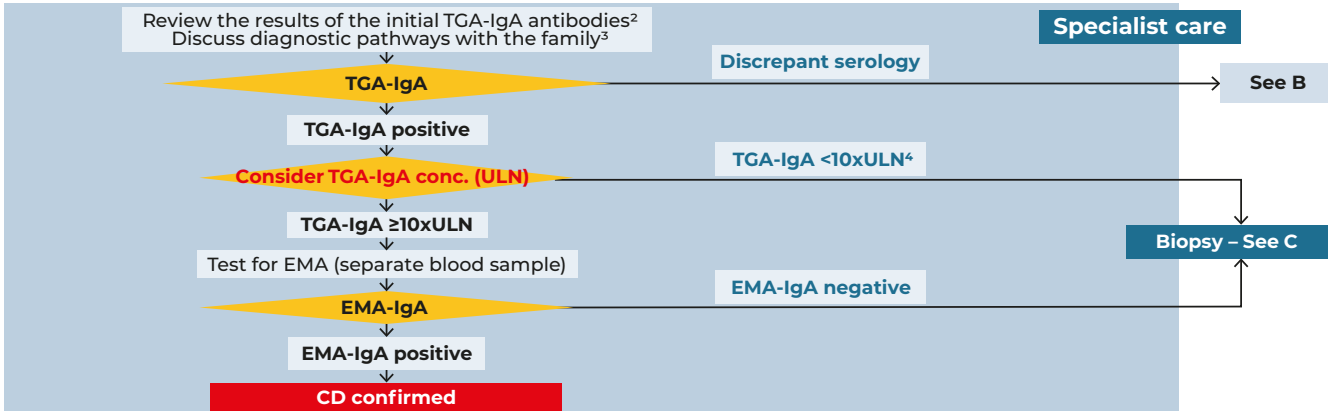


Figure 17. Diagnostic approach in children and adolescents with CD – initial care (A, B).

A.



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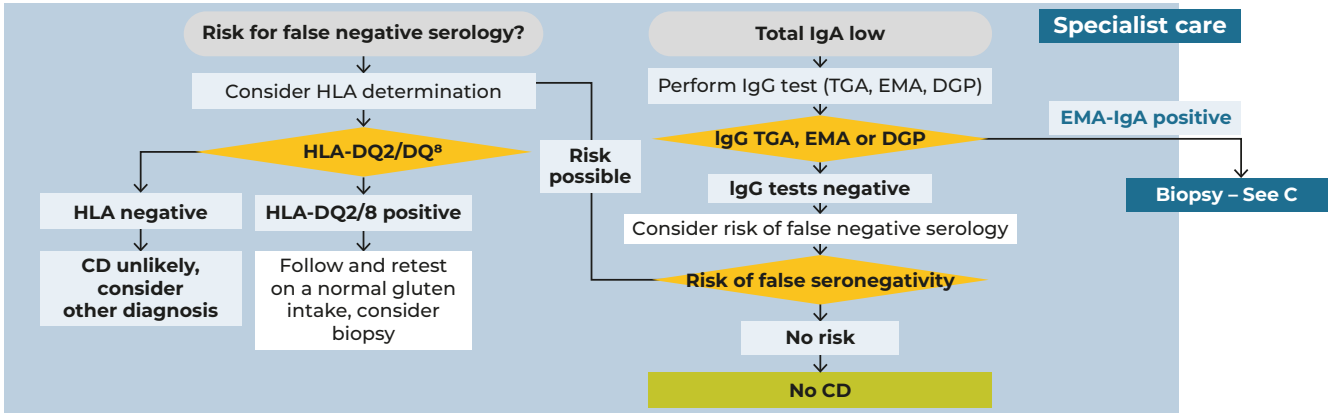
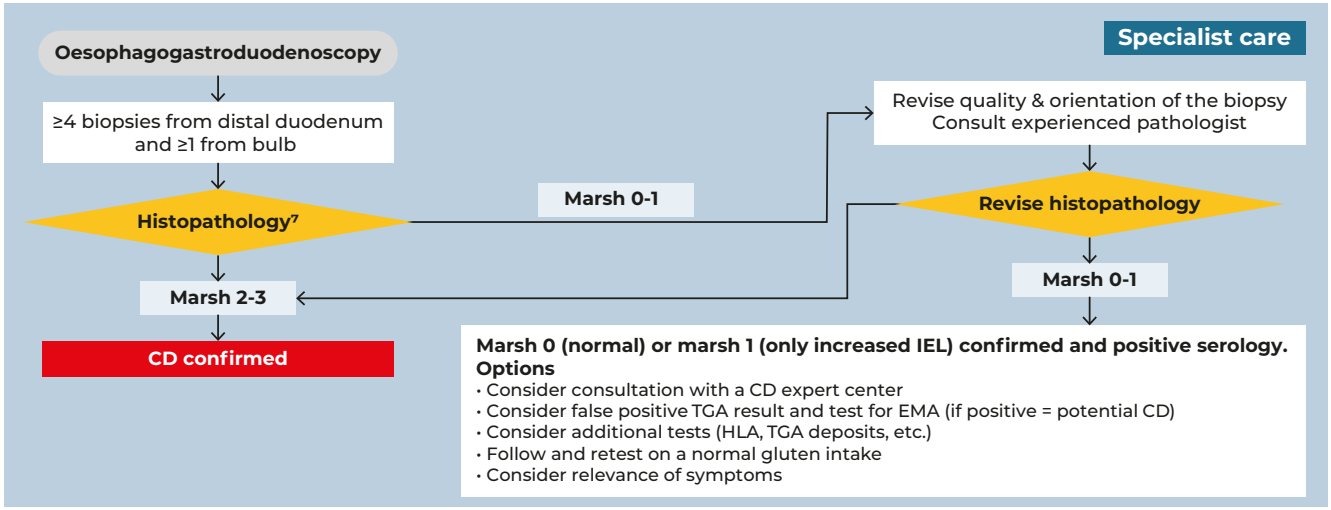


C.



Footnotes

1. Other than TGA-IgA, including point-of-care tests (POCT) and DGP.
2. Check the value also in relation to the cut-off and repeat the test if questionable or borderline. No need to retest if done with validated assay with calibration curve. Test with conventional TGA-IgA test if positive POCT and TGA has not been measured quantitatively.
3. Convey the message that the diagnosis of coeliac disease with or without biopsy confirms the need for a lifelong gluten-free diet and that re-evaluation after introduction of the diet would need prolonged re-exposure to gluten with a series of further investigations.
4. If TGA-IgA is only borderline positive confirm sufficient gluten intake and considerer retesting of TGA-IgA and EMA.
5. Low for age or <0.2 g/l above the age of 3 years.
6. For example, dermatitis herpetiformis, in which serology is frequently negative.
7. The cut-off for normal numbers of IEL is >25 cells/100 enterocytes.

Figure 18. Diagnostic approach in children and adolescents with CD – specialist care (A, B, C).

QUIZ

1. **Based on which test/s would you confirm CD?** (multiple answers possible)
   a) Faecal inflammation markers (e.g., calprotectin).
   b) Coeliac disease-specific antibodies stool test.
   c) Coeliac disease-specific serology tests.
   d) Upper endoscopy with biopsy.
   e) Colonoscopy with biopsy.
2. **Which of the following serological tests is used as the first-line test for the diagnosis of coeliac disease?**
   a) EMA (anti-endomysial antibodies)
   b) AGA (anti-gliadin antibodies)
   c) TGA (tissue transglutaminase antibodies)
   d) d-GP Ab (deamidated gliadin antibodies)
3. **A patient with symptoms and signs suggestive of coeliac disease tests negative for IgA TGA antibodies while consuming normal amounts of gluten. What is recommended?** (multiple answers possible)
   a) Consider other diseases.
   b) Determine total IgA and perform IgG t-TG Ab test if IgA deficient.
   c) Perform EMA IgA.
   d) Perform endoscopy with duodenal biopsy.
   e) Repeat the TGA IgA Ab test.
4. **Which conditions need to be fulfilled to consider diagnosing coeliac disease without intestinal biopsy?**
5. **Which classification is used for histological evaluation of biopsy specimens in CD?**
6. **Based on which test results would you be able to confirm coeliac disease?** (Normal TGA <16)
   a) Microcytic anaemia, normal biochemistry, TGA 67.
   b) 14.10.2022 TGA >200, 24.10.2022 EMA positive.
   c) Elevated liver enzymes, TGA 50, Marsh 2.
   d) TGA 12, Marsh 3, EMA negative

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7 Risk groups

OBJECTIVES:

- To identify coeliac disease risk groups.
- To understand the purpose of risk group screening.

Although coeliac disease is common, there are certain groups of people with a higher risk of developing the disease. It is very important to actively search for the disease in these groups. The initial step can be genetic testing for HLA-DQ2 or DQ8, and if the genetic risk is confirmed, these individuals need to be further tested with serological tests. Since coeliac disease can occur at any age, individuals with positive HLA-DQ2 or DQ8 haplotypes should be followed regularly to detect delayed-onset disease. However, current guidelines for diagnosing CD in children and adolescents propose performing TGA IgA as an initial test in risk-group children.

Risk group		% CD
First-degree relatives		10-20%
Other autoimmune disorders	Type-1 diabetes mellitus	3-12%
	Autoimmune thyroid disease	2-7%
	Autoimmune liver disorders	12-13%
Immunoglobulin A deficiency		2-8%
Chromosomal abnormalities	Down syndrome	5-12%
	Turner syndrome	2-5%
	Williams syndrome	up to 9%

CASE STUDIES

An 18-year- old boy was referred to the coeliac disease outpatient clinic for family screening since his sister had been diagnosed with coeliac disease 1 month previously. He explained that he had no specific complaints, except for problems with atopic dermatitis for many years. He had no abdominal pain, he defecated twice a day, and the stool was usually of normal consistency. His appetite was good and overall, he felt well. Serology for coeliac disease was highly positive.

A 4.5-year-old girl with Down's syndrome had been followed at the paediatric gastroenterology department since the age of 2 years. When she was first seen, she was in excellent general condition, thriving well and had regular and normal stools. Since Down's syndrome is associated with coeliac disease, coeliac serology was performed at the age of 2 and was negative. In addition, HLA DQ typing showed a positive genetic predisposition for coeliac disease (DQ 2.5). Screening for coeliac disease was repeated at the age of 3 and 3.5 years and again was negative. All that time, she ate gluten with no restrictions. At the age of 4.5 years, the patient was still in good clinical condition, gaining weight, with regular stools, and not complaining of abdominal pain. However, coeliac disease antibodies were ≥10 times the upper limit of normal and with positive endomysial antibodies from the second blood sample, coeliac disease was diagnosed with a no biopsy approach, according to the ESPGHAN 2020 guidelines.

A 12-year-old boy has been followed in the coeliac disease outpatient clinic for the past 5 years because of a family history of coeliac disease (his mother, aunt and cousin have coeliac disease). He missed the last two appointments for CD screening because of COVID restrictions and since he was feeling well all the time, his parents were not worried. A year ago, while playing football, he fell and suffered a compression fracture of Th9 and five months after that, he suffered a Th10 fracture when he fell from a standing position. His bone mineral density was found to be low; osteoporosis was confirmed, and the endocrinologist started treatment with bisphosphonates. At that time, repeat CD serology, showed elevated levels of TGA and positive EMA.

A 4-year-old girl was referred to our paediatric gastroenterology outpatient clinic because she was passing 3-4 watery stools per day. Prior to the first visit, the primary-care paediatrician performed anti-tissue transglutaminase antibodies, which were negative. At the examination in our clinic, the patient had abdominal distension, but otherwise, she was in a good condition, thriving well, with no signs of anaemia. As her IgA status was unknown, total IgA was ordered along with IgG class antibodies to deamidated gliadin peptide (DGP). The results showed IgA deficiency and highly positive IgG DGP antibodies. A duodenal biopsy showed Marsh IIIb and the diagnosis of coeliac disease was confirmed.

A 38-year-old woman visited her general practitioner because her daughter had been recently diagnosed with CD. She told the doctor that she has had abdominal pain for many years and that she had tried several diets, with no effect. When her daughter was diagnosed with coeliac disease, she was told that family members are an important risk group, so she requested testing for CD. Her GP ordered CD serological tests that were positive, and she was therefore referred to the gastroenterology outpatient clinic for further diagnostic procedures.

QUIZ

1. Which risk group has »the most risk« of developing CD?
2. What tests are usually performed when a risk group patient is referred to a paediatric gastroenterologist for the first time?
3. How often does the CD patient's brother (HLA-DQ3/HLA-DQ7) have to be screened for CD?
4. A person whose sister is coeliac is asymptomatic while consuming normal amounts of gluten. Previous genetic tests showed a genetic predisposition for coeliac disease. TGA antibodies are negative, total IgA is within the normal range. What would you recommend?
   a) Coeliac disease is not present at the given time. Continue normal diet, and schedule follow-up visit for repeated testing, especially if symptoms appear.
   b) Start a gluten-free diet. Coeliac disease is very likely.
   c) Tests are unclear. Perform a biopsy to confirm the diagnosis.
   d) Tests are unclear. Perform other serological tests (EMA or DGP Ab).

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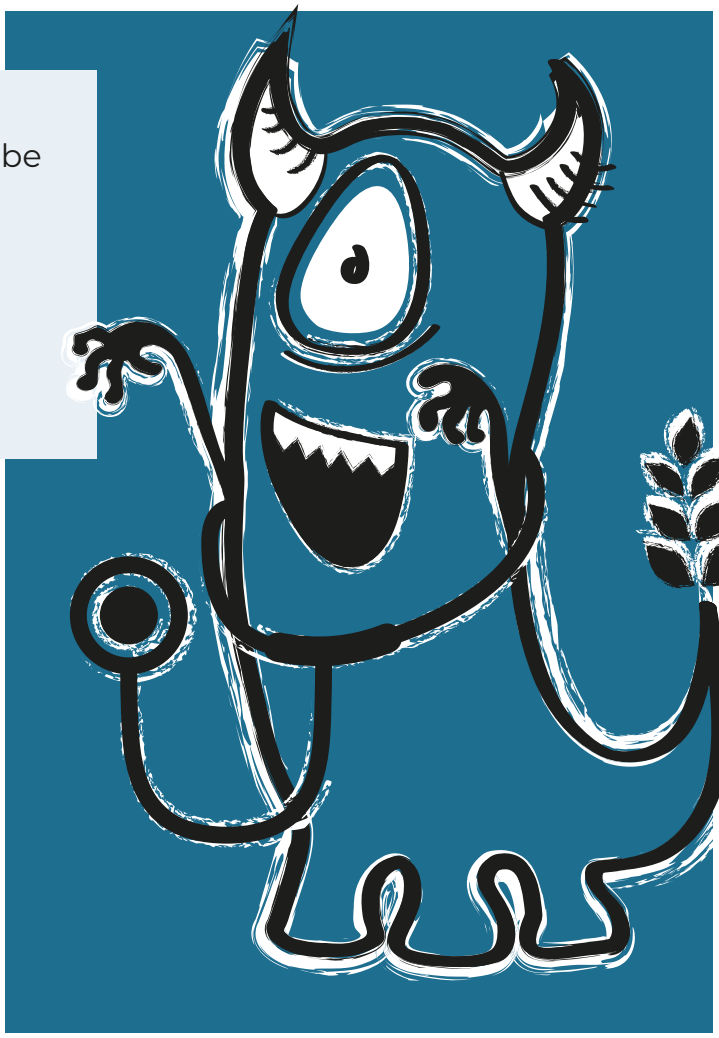
8 Treatment



OBJECTIVES:

- To learn how coeliac disease can be treated.
- To recognise gluten-free and gluten-containing cereals.
- To be able to identify hidden sources of gluten.
- To recognise the safe amount of gluten in gluten-free products.

The only available treatment for CD is a lifelong strict gluten-free diet, which can be started only after firm confirmation of the diagnosis by a specialist. Patients have to avoid all gluten-containing products. These include products from wheat and wheat cultivars, rye, barley, Khorasan wheat, triticale and bulgur. Due to the high likelihood of cross-contamination, it is also recommended that oats be avoided in many regions. It has been shown, however, that consumption of uncontaminated oats is safe and may improve the patient's quality of life. CD patients can safely consume naturally gluten-free foods and food that is produced specially for CD patients. There are many more naturally gluten-free foods than gluten-containing foods. Some are not related to grains at all, e.g., fruits, vegetables, animal products (meat, milk, and eggs), potatoes and roots. In addition, gluten-free cereals are naturally available, such as rice and corn. Of course, gluten-free cereals can be successfully used to substitute gluten-containing cereals. However, gluten can be found in many foods where it would not be expected (cheese, sweets, sauces, spices, some meat products, and many dairy products). These products may contain gluten in the form of a food additive that is supposed to enhance the properties of the food.

It is extremely difficult to maintain a strict gluten-free diet since gluten contamination is very common. "Hidden" gluten can be found in sausages, soups, sauces, ice cream and even non-food products, mainly medications, cosmetics, and toys. In addition, products that are made especially for CD patients can contain traces of gluten due to the cross-contamination of grains during grinding, storage, and the use of grains. Unintentional cross-contamination can be an important problem for patients and might lead to tissue damage, especially in the long term. Although a well-informed and compliant patient will manage to avoid 99.99% of gluten, it is

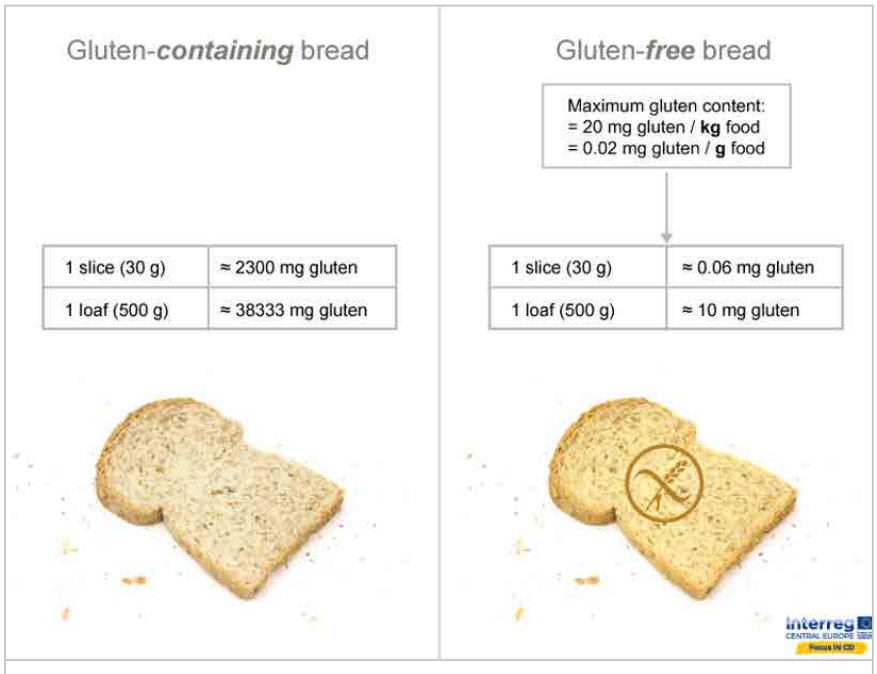


Figure 19. Comparison in the amount of gluten between regular gluten-containing bread (left) and gluten-free labelled bread (right).

impossible to maintain a diet 100% free of gluten. Therefore, the term "gluten-free" refers to an extremely low gluten intake that is below the threshold of what is considered harmful to coeliac patients. It has been found that a daily intake of up to 10 mg of pure gluten is very unlikely to cause any signs or symptoms in most patients. It is now widely accepted that the maximum level of gluten in foods may not exceed 20 ppm (parts per million; mg/kg). However, modern gluten-free products rarely contain more than 5 ppm of gluten.

When shopping, only pseudo-cereals or processed foods labelled with the crossed-grain symbol and ID number should be chosen, if available. This label guarantees that a food contains less than 20mg/kg gluten. The crossed-grain symbol is a registered trademark that is protected in many countries and is promoted by coeliac disease organisations worldwide. The AOECS (Association of European Coeliac Societies) provides a regularly updated list of certified products by member associations from different European countries.

On a strict GFD, the coeliac disease-associated antibody levels gradually normalise, and affected tissues usually fully recover. However, this may take several months, whereas symptoms may improve much faster, particularly in children. Although symptoms may also completely resolve in adults, gastrointestinal complaints may persist. The most common cause of persistent symptoms is ongoing gluten ingestion (inadvertent or voluntary). However, in some patients, mild abdominal discomfort may remain even on a strict gluten-free diet, although the CD-specific antibodies have normalised. In a very small proportion of patients, refractory CD causes persistent signs and symptoms.

For most patients, the following clinical effects and improvements will occur:

- Normalisation of antibody levels and regeneration of the intestinal mucosa.
- Decreased risk of long-term health complications (osteoporosis/osteopenia, lymphoproliferative disorders, autoimmune conditions).
- Weight normalisation if underweight.
- In children: catch-up growth and normal physical development.
- In women: improved pregnancy outcomes.

Although a GFD requires a thorough lifestyle change, patients should keep in mind that there are no side effects. Undertaking it carefully, under the supervision of a clinician and/or dietitian, the diet will benefit the overall health of coeliac disease patients.

Other possible therapies

A gluten-free diet, as the only treatment option for CD, is very challenging and restrictive. Therefore, efforts are being made to explore alternative therapies. These are classified by their mechanisms of action: modification of gluten, intraluminal therapy, immunomodulation, intestinal permeability, and modulation of the adaptive response. The immunogenic content of gluten could be decreased, for example, by using genetically modified wheat or by intraintestinal gluten digestion using glutenases (peptidases). Using binder drugs, the gluten in the gut lumen could be sequestered before it is digested into immunogenic peptides and absorbed. Another possible approach would be to prevent the uptake of digested gluten through intestinal epithelial tight junctions using a zonulin antagonist or to prevent the enhancement of the immunogenicity of digested gluten by the intestinal tissue transglutaminase using tissue transglutaminase inhibitors. There has also been research into how to prevent downstream immune activation after the uptake of gluten immunogenic peptides through the intestinal mucosal epithelial layer, for example, by using HLA-DQ2 blockers, which prevent the presentation of gluten-derived antigens. However, all these therapies have several important limitations due to complications or the lack of a complete response, hence most are still in the pre-clinical phases.

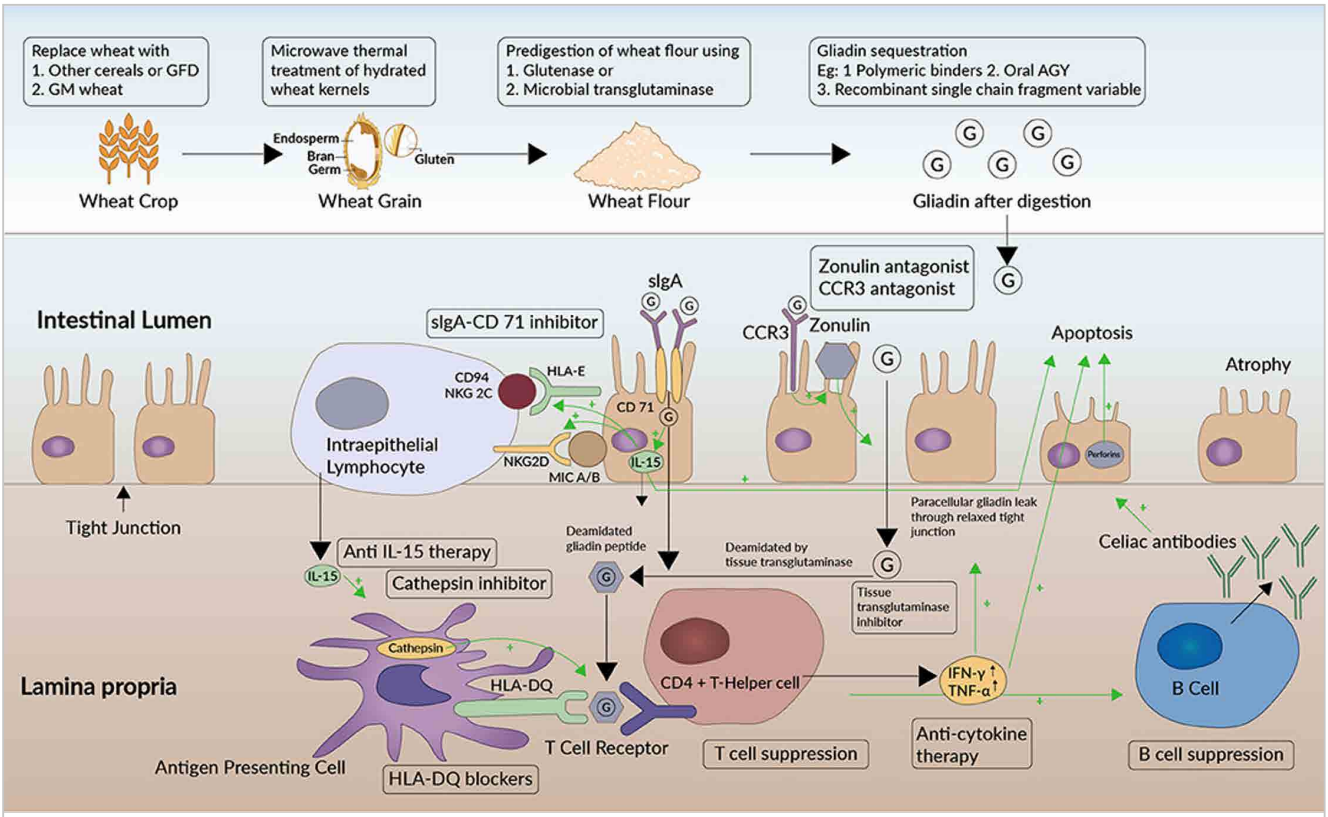


Figure 20. Possible new therapies for coeliac disease (Yoosuf S, Makharia GK. Front Pediatr.2019).

QUIZ

1. What kind of gluten-free diet is recommended for patients with coeliac disease to prevent serious complications of the disease?
   a) Diet with reduced gluten intake.
   b) Strict gluten-free diet for a short period (a few months) and then reduced gluten intake.
   c) Strict gluten-free diet for a short period and then a normal diet
   d) Strict gluten-free diet for a longer period (several years) and then reduced gluten intake.
   e) Strict gluten-free diet for a longer period and then a normal diet.
   f) Strict lifelong gluten-free diet.
2. Should you start a gluten-free diet after positive CD-specific antibody tests but before the diagnosis is confirmed (by confirmatory antibody testing or intestinal biopsy)?
3. How much gluten can gluten-free products contain?
4. Which of the following grains do you think should be excluded by patients with CD because they contain gluten? Please, underline them.
   WHEAT, BUCKWHEAT, RICE, BARLEY, MILLET, OATS, TRITICALE, RYE, KAMUT, SPELT, MAIZE, BULGUR, SOY.
5. Are there other treatment possibilities besides a gluten-free diet?

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9 Follow-up

OBJECTIVES:

- To learn how coeliac disease patients should be followed.
- To understand which investigations need to be performed during follow-up visits.
- To learn how the transition to adult care should be organised.

After the diagnosis of coeliac disease is established, patients must follow a strict gluten-free diet, so consultation with a dietitian is advisable. Dietary counselling may be the best instrument not only for maintaining patient adherence, but also to evaluate the patient's nutritional status, to optimise and nutritionally balance the gluten-free diet and to offer support to families facing many challenges of the new dietary lifestyle.

The first follow-up visit with the paediatric gastroenterologist should be performed 3-6 months after diagnosis. Subsequent visits should be every 6 months until normalisation of TGA levels, and every 12–24 months thereafter. The effectiveness of treatment is assessed by the improvement in symptoms and signs and normalisation of CD-specific antibodies, which might take several months. The titres of TGA IgA antibodies can be expected to fall below the cut-off of the normal values within 12 months after starting a strict gluten-free diet. In many patients, they may normalise much earlier. It is important to assess adherence to the gluten-free diet.

During the follow-up visit, patients should be evaluated for gastrointestinal and extraintestinal signs and symptoms and anthropometric measurements. Special attention must be paid to children's growth and development (physical, psychosocial, and pubertal development). The level of TGA IgA should be measured together with complete blood cell count, micronutritional status (haemoglobin, iron, vitamin B12, and vitamin D levels) and liver enzyme measurements if found abnormal at diagnosis. Any abnormality should be followed, and deficiencies corrected until normalisation. If abnormalities persist, additional diagnoses should be considered and appropriately investigated. Screening for thyroid disease with TSH and thyroxine (and autoantibodies if indicated) may be considered during follow-up after clinical evaluation. Routine bone-density screening is not recommended. Bone mineral density should be measured at least once after initiation of the gluten-free diet if one of the following applies:

- CD was diagnosed during adulthood (BMD measurement to be scheduled about one year after starting a GFD)
- Other risk factors for osteoporosis are present (e.g., corticosteroid therapy for other co-morbidities)
- The adherence to the strict gluten-free diet is poor.

The lack of decreasing IgA-TGA levels after 6–12 months on a GFD or persisting positive IgA-TGA levels should be assessed by carefully reviewing dietary compliance and testing IgA-TGA using the same test from the same manufacturer. Routine assessment of mucosal healing by small-bowel biopsies is not recommended in children with CD following a GFD. Re-biopsy is considered only in selected CD cases, based on specific clinical grounds, for example, if there are doubts about the original diagnosis or suspicion of the occurrence of an additional condition, for example, other possible concomitant enteropathies, such as Crohn's disease, autoimmune enteropathy, small-bowel bacterial overgrowth, cow's milk protein allergy and pancreatic insufficiency.

For better adjustment to the life changes associated with the presence of chronic disease, some patients will also benefit from psychological counselling.

Transition to adult care

An adolescent with CD is usually transferred to adult care at the age of 18 years. The transfer should be structured and, at a minimum, include a transition letter or "coeliac passport" providing data on the diagnosis, follow-up, anthropometric data, possible comorbidities, and dietary adherence level.

QUIZ

1. When should the first follow-up visit be performed?
2. How often should patients with coeliac disease be followed when stable?
3. 10 years after the diagnosis of coeliac disease was confirmed by serology and biopsy, the patient is still without symptoms since he is on a strict gluten-free diet. Serological tests are negative. What is recommended?
   a) Coeliac disease is no longer present. Diet is no longer needed.
   b) The clinical picture and serological tests suggest good disease control. Continue the diet.
   c) A control biopsy is needed to confirm intestinal healing and if so, gluten can be re-introduced stepwise into the patient's diet.
   d) A gluten challenge for six months is recommended, and serological tests should be repeated after this period.
4. Are repeated intestinal biopsies required after diagnosing coeliac disease to follow patients' responses?

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10 Complications

OBJECTIVES:

- To be able to identify possible complications of coeliac disease.
- To understand the importance of the timely diagnosis of coeliac disease.

When a patient is diagnosed with coeliac disease and maintains a strict gluten-free diet, usually all symptoms resolve. However, if the gluten-free diet is not adhered to strictly or if the disease is diagnosed in adults or with substantial delay, the risk of complications increases. Among the most dangerous complications is malignant lymphoma of the small intestine, although complications can also affect various organ systems, such as the reproductive, neurological, cardiovascular, and haematological systems. Psychiatric disorders can also occur. Low bone mineral density can result in bone fractures. These complications, which rarely present in children, can be irreversible and the introduction of a strict gluten-free diet might not bring complete resolution of the damage already present.

Therefore, the development of the long-term complications of undiagnosed and/or untreated coeliac disease is another important factor that calls for early detection (and appropriate treatment) of the disease in all symptomatic patients as well as in patients that belong to the so-called risk groups for coeliac disease.

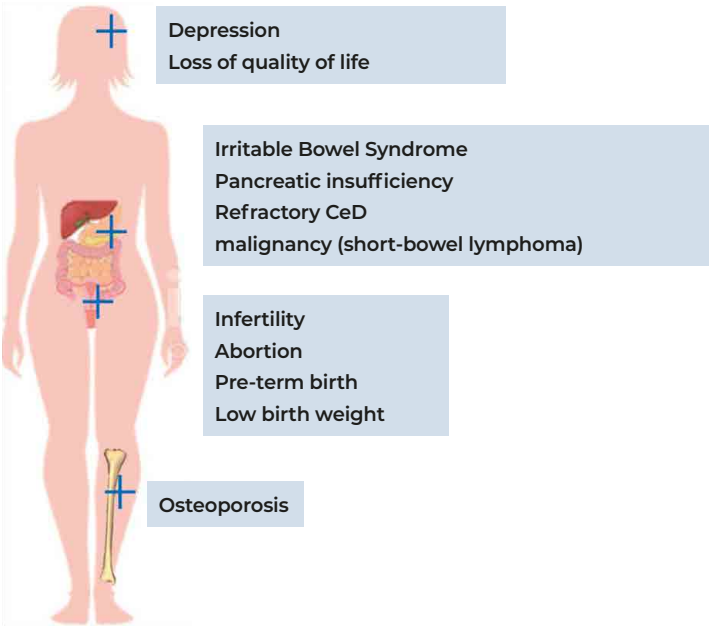

Figure 21. Possible complications of untreated coeliac disease.

PATIENT STORIES

A boy who was operated for Hirschsprung's disease as an infant was admitted to the surgical department at the age of 3 years due to severe abdominal distension, failure to thrive and anaemia. Obstruction was suspected and surgical revision was undertaken. Afterwards, the anaemia was corrected, and he started to gain weight, although his weight gain was still not satisfactory. This was attributed to the socially deprived conditions in which he lived. A few months later, he was again seen by the surgeon for an uncomplicated arm fracture that occurred after a mild trauma. His arm was placed in a cast, and the bone healed well. However, at the age of 4 years, he was readmitted to hospital for a broken leg requiring surgery. Blood tests revealed anaemia and given the patient's history, coeliac serology was ordered, which came back highly positive.

A 43-year-old man was referred to the emergency room due to vomiting and weight loss. He explained that he had been feeling unwell for the past six months, had no appetite, and had lost 15 kg. He had been vomiting a lot and he also had frequent abdominal pain. Twenty-five years previously, he had been diagnosed with coeliac disease, but he had not been very compliant with the diet. During the examination, he complained of abdominal pain, and he looked undernourished. Laboratory blood tests showed hypoalbuminaemia with electrolyte disturbances. Serological tests for coeliac disease were highly positive. An oesophagogastroduodenoscopy was performed, which showed active coeliac disease, and a subtotal stenosis of the distal part of the duodenum was found on X-ray passage. A deep duodenoscopy showed tumour formation. Histology revealed an adenocarcinoma, most likely as a complication of untreated coeliac disease. Surgical resection was performed.

QUIZ

1. **Which of the following may be a complication of untreated (or undiagnosed) coeliac disease?** (multiple answers possible)
   a) Anaemia
   b) Osteoporosis
   c) Intestinal lymphoma
   d) Colon cancer
   e) Cardiac problems
   f) Renal insufficiency
   g) Inflammatory bowel disease
   h) Infertility
2. **Which complication of CD can be resolved with a gluten-free diet?**
   a) Microcytic anaemia
   b) Osteopenia
   c) Intestinal lymphoma
   d) Epilepsy
3. **Which patients' growth retardation/small stature can still be resolved with a gluten-free diet?**
   a) A 4-year-old girl
   b) A 19-year-old boy
   c) A 34-year-old man
   d) A 15-year-old girl

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11 Quality of life of coeliac disease patients

For some patients, the time from the first symptoms to getting a coeliac diagnosis can be a long and hard journey, but for all of them, the real challenge starts after the diagnosis. Answers to the questions What is gluten and how can I avoid it? What can I eat? Where can I eat? How can I prepare gluten-free food? How can I ensure a safe environment in school or kindergarten? What are my rights? can be found on the web and social media, but one has to be aware that those sources can sometimes be unreliable.

Coeliac societies are organisations where patients can find answers to their questions, as well as practical help and support while living with coeliac disease.

From the patient's perspective, key features relevant to adherence to gluten-free diets are:

- Accepting the disease and the "loss" of some aspects of normal life, due to the restrictions of a gluten-free diet.
- Understanding the basics of coeliac disease.
- Understanding what a gluten-free diet is and what a nutritionally balanced diet is.
- Knowing what (industrial) products can be used in gluten-free diets and the availability of those products.
- The affordable price of gluten-free products.
- Knowing what the critical points are in preparing gluten-free meals.
- Having key skills to prepare homemade gluten-free products (bread, cakes, pastry, etc.) and meals generally.
- Having the option to eat safely outside the house, especially in educational institutions (kindergartens, schools), hospitals, homes for the elderly, etc.
- Accepting the fact that a person/child with coeliac disease is different because of his/her special dietary needs and that he/she also has special educational needs.
- Having a supporting/inclusive environment where one feels safe, accepted, and equal to others. That especially refers to kindergartens and schools because children are a vulnerable population. School programmes and curriculums, as well as materials and methods used, should be adjusted to CD patients. Children and educational workers should also be sensitive to the needs of children with CD.

All these features have to be considered in comprehensive and multidisciplinary healthcare for CD patients. Various stakeholders must be included to provide help and support and protect the mental and physical health of coeliac patients and enable them to live normal functional lives, which will, in the end, result in a decrease in public health issues and high costs related to nonadherence to a gluten-free diet.

12 Clinical cases

1. A primary-care paediatrician calls the paediatric gastroenterology outpatient clinic asking for consultation. He presents a case of an 11-year-old boy on a regular diet, with abdominal pain that occurs 2-3 times a month. CD serological tests were performed one week previously. The results are as follows: total IgA – normal; TGA 19 (upper level of normal 16). What would you recommend?

2. A mother and her 4-year-old girl come to the outpatient clinic because of the girl's diarrhoea. She tells you, that the girl defecates 3 times per day, and the stool is soft, but not entirely liquid. She has already tried a gluten-free diet at home and ever since the girl has been on the diet, she defecates once per day. What would you recommend?

3. The mother of a newly diagnosed CD patient comes to the coeliac disease outpatient clinic for family screening of her 13-month-old son. Her older daughter had been diagnosed with CD 5 months previously. What investigations would you perform and what instructions will you give to the mother?

4. A 17- year- old boy was admitted to the hospital for planned upper endoscopy because of suspicion of H. pylori infection (positive stool test). An endoscopy revealed nodular gastritis. The histology results confirm H. pylori infection. Marsh 3a changes were observed in duodenal biopsies. You schedule a follow-up visit to test for coeliac disease. TGA and EMA were both found to be negative. What would your decision be?

5. A 10- year- old girl was referred to the outpatient clinic because of weight loss and growth retardation. Her mother tells you that the girl has always been the smallest in her class, and despite eating well, she has not gained weight appropriately. She has never complained of abdominal pain, but sometimes she has felt a bit nauseous after lunch, regardless of what she has eaten. She is also very tired all the time and sometimes a bit restless. Laboratory results showed TGA 200 (upper level of normal 16), and EMA is positive. What would you suggest to the girl and her mother?

6. A 4-year-old girl was referred to the outpatient clinic because of abdominal pain and constipation. Her mother explained that the girl has frequently complained of abdominal pain, especially in the evening during the week. The abdominal pain persists for a few minutes and is usually self-limiting. She defecates once every three days and the stools are usually hard in the form of small bobs. She has already tried a diet without cow's milk proteins, but no obvious changes were observed. The mother then explains that she had been reading about a gluten-free diet and had decided to give it a try. When you ask what the girl usually eats, her mother tells you that she usually eats cornbread or spelt pasta. They have stopped eating white bread at home. Since they excluded white bread, the girl has been doing better, so the mother would like to have a certificate that her daughter has coeliac disease so she can receive gluten-free food in kindergarten. What would you tell the mother?

13 Quiz results

2. HISTORY OF COELIAC DISEASE

1) A long time ago, there was no gluten in the human diet. Man was a hunter and a gatherer, so he ate fruits, nuts, tubers and occasionally the meat of hunted animals. It was only after the end of the last ice age that he started growing food and the first types of cereals appeared.
2) The invention of the jejunal biopsy device, with which a biopsy of the distal duodenum was successfully performed for the first time.

3. EPIDEMIOLOGY

1) 1%.
2) The disparities in the awareness of CD, variations in healthcare resources and diagnostic protocols used to detect CD.

4. AETIOLOGY:

1) b
2) HLA DQ2/DQ8
3) 30-40%
4) c, d, e

5. CLINICAL PRESENTATION

1) b, d, e
2) In very young children, signs and symptoms of malabsorption are more common than in older children and adolescents, in whom abdominal pain is the most common symptom. In adults, the disease often does not present with characteristic signs and symptoms, but with extraintestinal manifestations or serious complications.
3) Early childhood (1-4 years of age), puberty, and the period of lactation after giving birth in women.
4) Classical CD presents with symptoms and signs of malabsorption: diarrhoea, steatorrhoea, bloating, growth retardation or weight loss, anaemia, neurological disorders due to vitamin B deficiency, osteopenia due to vitamin D and calcium deficiency.
5) Dermatitis herpetiformis. Diagnosis: skin biopsy, showing pathognomonic granular deposits of immunoglobulin A in the papillary dermis. Damage to the intestinal mucosa can also be found. Patients with severe skin symptoms may need special medications in addition to a gluten-free diet.
6) a, c

6. DIAGNOSIS

1) c, d
2) c
3) a, b, c, d, e
4) No-biopsy approach: TGA-IgA > 10 times the upper limit of normal, EMA positive in a second blood sample, a paediatric gastroenterologist is involved in the process.
5) Marsh – Oberhuber
6) b, c

7. RISK GROUPS

1) First-degree family members of CD patients.
2) TGA IgA. Genetic testing can also be considered.
3) Screening is not necessary since he has no genetic predisposition to the development of CD.
4) a

8. TREATMENT

1) f
2) No, the diet can be initiated when the diagnosis is confirmed.
3) Below 20 ppm.
4) Grains that need to be excluded: WHEAT, BARLEY, TRITICALE, RYE, KAMUT, SPELT, BULGUR.
5) No.

9. FOLLOW-UP

1) 3-6 months after diagnosis.
2) Once every 12-24 months.
3) b
4) No.

10. COMPLICATIONS

1) a, b, c, e, h
2) a, b
3) a

14 Clinical cases results

1. Test again in approx. 3-6 months and if TGA positive, perform upper endoscopy if needed (according to the antibody level). Advise a normal, gluten-containing diet until the end of the diagnostic process.

2. To confirm the diagnosis of CD, gluten in sufficient quantity (10-15g/day) must be reintroduced into the diet for at least three months. Then, repeat the tests and proceed according to the guidelines. Gluten reintroduction can be safely done only at a specific age to prevent the harmful effect of gluten on a child's growth.

3. TGA IgA should be performed alongside total IgA determination, and you may also consider genetic testing. You need to explain to the mother that there is a risk of her younger son developing CD, so if the genetic tests are positive, he will be screened approximately annually, or sooner if symptoms/signs suggestive of CD appear. The boy should not be on a gluten-free diet in the meantime.

4. You prescribe eradication therapy for *H. pylori* infection. CD serology tests should be performed again in six months (TGA IgA) and repeated upper endoscopy should be considered after that (unless eligible for the no-biopsy approach). Until these tests, the boy should eat a regular, gluten-containing diet.

5. The girl probably has coeliac disease. You explain the disease and the diagnostic process. Due to the very high levels of TGA, she is eligible for the no-biopsy approach, and you schedule her for the second blood withdrawal for EMA testing.

6. You can safely perform CD serological testing since the girl was not really on a gluten-free diet. If the tests are positive, proceed according to the diagnostic algorithm. You advise about treatment for constipation.

List of used abbreviations

AOECS	Association of European Coeliac Societies
AGA	Anti-gliadin antibodies
DGP	Deamidated gliadin peptide
DGP Ab	Deamidated gliadin peptide antibodies
EMA	Anti-endomysial antibodies
ESPGHAN	European Society for Paediatric Gastroenterology, Hepatology and Nutrition
HLA	Human leukocyte antigen
IEL	Intraepithelial lymphocytes
IgA	Immunoglobulin A
IgE	Immunoglobulin E
IgG	Immunoglobulin G
IgM	Immunoglobulin M
POCT	Point-of-care-testing
ppm	Parts per million
RC	Refractory celiac disease
TGA	Tissue transglutaminase antibodies
TSH	Thyroid-stimulating hormone

E-learning course for healthcare professionals and patients

Within the CD SKILLS (Interreg Danube Transnational Programme) project two innovative e-learning tools have been implemented, one for healthcare professionals and the other for patients. The e-learning tools are an upgrade of the existing tools developed within the Focus IN CD project (Interreg Central Europe Programme) and updated in accordance with the new ESPGHAN (European Society of Paediatric Gastroenterology, Hepatology and Nutrition) guidelines for the management of coeliac disease published in 2020. The e-learning tools, which are available in English, German, Slovenian, Hungarian and Croatian, have been updated, and versions have been added in Romanian and Czech.

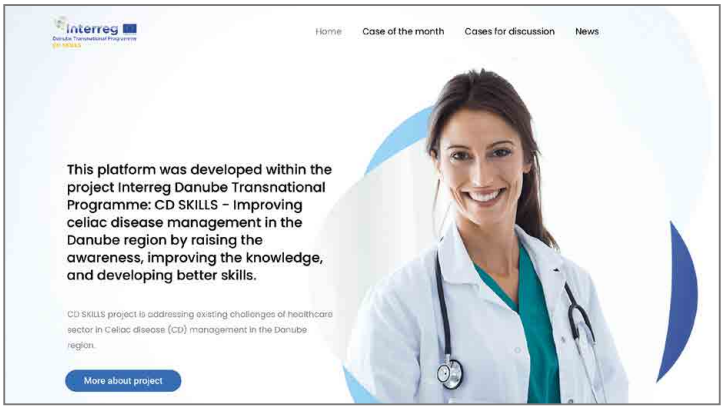
E-tools are available at : www.celiacfacts.eu.

The postcard promoting coeliac disease e-learning tools for patients and healthcare professionals.

CD SKILLS transnational information exchange network for healthcare professionals

CD SKILLS transnational information exchange network - an open-access web-based platform designed for healthcare professionals, was established within the project. The aim of the platform is to exchange knowledge and information, discuss challenging cases and share problems in the field of coeliac disease with other members of the network. Each month, an interesting and instructional clinical case is presented as a "case-of-the-month " presentation. The second part of the platform is dedicated to "cases for discussion" where partners and other healthcare professionals can present and discuss challenging coeliac disease cases, ask questions and share problems.

Visit the platform at: https://cdskills.eu/.



Exchange platform to share the challenges of coeliac disease.

CD SKILLS publications

During the two and a half years of the CD SKILLS project, four publications aimed at coeliac patients, healthcare professionals, caterers and medical students have been prepared to raise knowledge, increase competences and foster uniformity in the management of coeliac disease (CD).

All brochures are available in the languages of the partners on the project website: https://www.interreg-danube.eu/approved-projects/cd-skills (Library).

Brochure for healthcare professionals "Hand in hand with celiac disease"


UKC
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ŽIVOT S CELIJAKIJOM

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Children's Hospital Zagreb

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