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TRABALHO FINAL
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Abstract

Celiac disease (CD) is a systemic disease that is triggered by gluten ingestion, in genetically predisposed individuals. It manifests as an autoimmune small bowel enteropathy associated with specific circulating autoantibodies and human leucocyte antigen haplotype (HLA-DQ2 or HLA-DQ8). It afflicts roughly 1% of the population, even though the majority of patients remain undiagnosed.

While children with CD manifest with diarrhea and malabsorption, adults can be paucisymptomatic and present extra-intestinal manifestations such as anemia, osteoporosis and abnormal liver tests. Although CD screening is not recommended for the general population, it should be focused on high-risk groups.

CD diagnosis is challenging and relies on serological tests, duodenal histology, and genetic testing. Treatment rely on lifelong gluten free diet.

An increased medical awareness, biopsy sparing diagnostic algorithms and alternative effective treatments should be the goals for the future in terms of CD.

Keywords: Celiac disease, HLA, serological tests, duodenal histology, diagnostic challenges

Resumo

A doença celíaca (DC) é uma doença sistémica desencadeada pela exposição ao glúten em doentes geneticamente susceptíveis. Manifesta-se como uma enteropatia auto-imune associada a auto-anticorpos e aos haplótipos HLA-DQ2 ou HLA-DQ8.[1]

A primeira referência a uma doença malabsortiva crónica que leva a um estado de desnutrição remonta a Aretaeus, na Cappadocia, no seculo III d.C, contudo, a primeira descrição clínica moderna da DC data de 1888, no artigo de Samuel Gee, “On the coeliac affection”.[2–4]

De acordo com uma meta-análise recente, a prevalência de DC é 1,4% por serologia e 0,7% por biopsia. Nos últimos 20 anos registou-se um aumento de 33% na prevalência de DC, possivelmente associado a factores ambientais.[5, 6] Acresce que a prevalência está seguramente subestimada, admitindo-se que por cada doente diagnosticado há quatro não diagnosticados.[7]

A presença do haplotipo HLA-DQ2/8 é o principal factor de risco para a DC sendo condição necessária, ainda que não suficiente, para o desenvolvimento da doença. Cerca de 40% da população geral apresenta um dos haplótipos, contudo, só 2 a 3% destes vêm a desenvolver doença.[8]

Vários factores ambientais têm sido estudados como possíveis factores de risco ou protectores na DC, como a idade de introdução do glúten, doenças infeciosas e o aleitamento materno.[9–11] A literatura não é consistente relativamente a uma possível associação entre DC e a idade de introdução do glúten,[12, 13] não parecendo haver associação com o aleitamento materno.[12, 14–17] As infecções gastrointestinais (por *rotavírus* e *adenovírus* em crianças e *Campylobacter* nos adultos) e respiratórias recorrentes (nos primeiros 18 meses de vida) têm sido associadas à DC, contudo o nível de evidência nesta matéria é fraco.[9, 10, 18, 19]

Entre os grupos de risco para DC incluem-se os familiares em primeiro grau [20], indivíduos com diabetes mellitus tipo 1 [21], outras doenças auto-imunes [22], doentes com deficiência seletiva de IgA [23] e cromossomopatias como S.Down [24] e S.Turner [25].

A fisiopatologia da DC centra-se numa intensa resposta imunológica precipitada pela ingestão de glúten (presente em cereais da família Gramineae como o trigo, centeio e cevada) que leva a lesão e inflamação intestinal com consequente má-absorção.[26]

O termo glúten é amplamente usado para definir proteínas da família Gramineae, contudo, estritamente falando, glúten só se refere ao trigo. As proteínas do centeio designam-se secalinas e as da cevada hordeínas.[27–29]

A resistência dos polipéptidos de glúten às proteases gastrointestinais [29] é fundamental para o potencial patogénico da doença, já que o complexo major de histocompatibilidade II (CMH-II) só apresenta péptidos com mais de 9 aminoácidos.[30]

O primeiro passo na patogénese da doença é a passagem dos polipéptidos através da barreira epitelial permitindo a sua exposição às células apresentadoras de antigénios na lâmina própria. Esta passagem pode ocorrer em situações que aumentem a permeabilidade intestinal ou mediante vias transcelulares, como a mediada por receptores CD71 na superfície apical dos enterócitos, que se ligam a complexos glúten-IgA secretória.[8, 28, 31–33]

Na lâmina própria o glúten é desaminado pela transglutaminase tecidual (tTG), o que aumenta a estabilidade da ligação ao CMH-II.[30, 34] Cerca de 90% dos doentes expressam o HLA-DQ2.5 (alto risco para DC) e os restantes 10% os HLA-DQ2.2 ou HLA-DQ8 (baixo risco).[35] Os péptidos desaminados ligados ao CMH-II das células apresentadoras de antigénios são apresentados aos linfócitos T CD4+, activando-os.[36] Estes linfócitos adquirem um fenótipo pró-inflamatório libertando citocinas como o interferão-γ e a IL-21 que activam os linfócitos T CD8+ , lesando os enterócitos.[35] Os linfócitos T CD4+ activados secretam também factor de necrose tumoral-α e factor de crescimento de queratinócitos que contribuem para a atrofia das vilosidades e hiperplasia das criptas.[37, 38] A activação dos linfócitos T CD4+ promove ainda a proliferação de linfócitos B e sua diferenciação em plasmócitos e subsequente produção de auto-anticorpos.[35, 39]

A DC pode apresentar uma grande variedade de sintomas, tanto gastrointestinais como extra-intestinais. As manifestações gastrointestinais mais comuns são a diarreia (35%), dor abdominal (28%), perda de peso (22%) [8, 40], obstipação crónica (20%) e distensão abdominal (20%).[8, 9] Estas manifestações são geralmente mais comuns em crianças enquanto que os adultos tendem a ser paucissintomáticos.[9] As manifestações extra-intestinais mais comuns são a osteopénia (50-70%), anemia (32%), artralgia (29%), fadiga (26%) e alterações neurológicas (20%).[8, 41]

Deve ser pesquisada DC nos doentes de alto-risco bem como os que apresentam défice de ferro, acido fólico e vitamina B12 de etiologia desconhecida, doentes com síndrome do intestino irritável, úlceras orais persistentes, sintomas gastrointestinais persistentes, perda de peso, atraso no crescimento, infertilidade, osteopénia, alterações hepáticas e sintomas neurológicos não explicados por outra patologia.[42]

O diagnostico de DC assenta em 3 eixos fundamentais: testes serológicos, histologia duodenal e testes genéticos. [43]

A IgA anti-transglutaminase tecidual é o teste serológico de primeira linha devido à sua elevada sensibilidade, devendo ser testado em simultâneo com o doseamento da IgA sérica, para excluir falsos negativos nos doentes com défice de IgA. [26, 44] A IgA anti-endomísio é o teste com maior especificidade e deve ser usado como teste confirmatório.[45, 46] No caso de deficiência de IgA, o teste preferencial é a IgG anti-

gliadina desaminada.[45–47] Os testes devem ser realizados sob dieta com glúten para evitar falsos negativos.[48]

Depois de um teste serológico positivo todos os doentes devem realizar uma endoscopia digestiva alta com biopsia duodenal que, se apresentar achados histológicos compatíveis com DC, confirma o diagnóstico. [49, 50] Estas biopsias devem também ser realizadas em doentes seronegativos se a suspeita clínica for elevada. [48] Uma vez que o duodeno é afectado de forma descontinua são recomendadas, no mínimo, 4 biopsias pós bulbares e uma ou duas do bulbo, de modo a aumentar a sensibilidade da histologia. [48, 51] Os achados histopatológicos mais típicos da DC são a linfocitose intraepitelial, a hiperplasia das criptas e a atrofia das vilosidades. Estas alterações são classificadas segundo os critérios de Marsh modificados.[44, 52]

O papel do teste genético no diagnóstico tem lugar essencialmente na exclusão da doença em casos duvidosos, visto ter um valor preditivo negativo para DC de 100%. [53]

O diagnóstico da DC apresenta diversos desafios, como são o caso da DC seronegativa, da DC potencial, da sensibilidade ao glúten não celíaca (SGNC) ou das diversas patologias que também cursam com atrofia das vilosidades e linfocitose intraepitelial. [44]

A DC seronegativa refere-se a doentes que apresentam serologias negativas, mas histologia positiva e HLA de risco, correspondendo a 2% dos doentes com DC. Para confirmar DC seronegativa os doentes devem também apresentar melhorias após a instituição de dieta sem glúten. [54–56]

Os doentes com testes serológicos positivos, mas mucosa normal ou linfocitose intraepitelial são designados como tendo DC potencial. O doente pode ou não ter manifestações e pode ou não vir a desenvolver enteropatia no futuro. [49, 57]

A SGNC carateriza-se pelo aparecimento de sintomas, intestinais ou extra-intestinais, semelhantes aos da DC após a ingestão de glúten, num doente sem DC ou alergia ao trigo. Os sintomas surgem rapidamente (horas a dias) após a ingestão de glúten e desaparecem também rapidamente (horas a dias) após a sua exclusão da dieta. [58–60] A SGNC apresenta tanto histologia como serologia negativa e não tem biomarcadores conhecidos, assim sendo, o seu diagnostico é clínico. [61, 62]

O único tratamento com eficácia comprovada para a DC é a dieta sem glúten. Esta dieta implica a evicção de trigo, centeio, cevada e por vezes também de aveia. [43, 63] A adesão à terapêutica é baixa (17-48%) e a mortalidade dos doentes que não a cumprem é 5 vezes superior à dos doentes que aderem à terapêutica.[64–66] Depois de iniciar a dieta sem glúten a generalidade dos sintomas melhora no primeiro mês e desaparece no sexto.[67] A maioria dos doentes torna-se seronegativo ao fim de 6 meses [68, 69], no entanto, a normalização histológica é mais morosa, podendo demorar entre 2 e 5 anos. [70]

Em conclusão, a DC é uma patologia sub-diagnosticada, com um aumento da prevalência nas últimas décadas, e para a qual o único tratamento eficaz é a dieta sem glúten. O diagnóstico é um desafio não só pelas diversas formas de apresentação da doença como pelo número de patologias que partilham achados histológicos com a DC.

Palavras-chave: Doença celíaca, HLA, testes serológicos, histologia duodenal, desafios diagnósticos

O Trabalho Final exprime a opinião do autor e não da FML.

List of abbreviations

ACG : American College of Gastroenterology

AGA : Anti-gliadin antibody

APC : Antigen-presenting cells

CD : Celiac disease

DGP : Deaminated gliadin peptides

EATL : Enteropathy associated T-cell lymphoma

EMA : Anti-endomysial antibody

ESPGHAN : European Society for Paediatric Gastroenterology Hepatology and Nutrition

ESsCD : European Society for the Study of Coeliac Disease

GFD : Gluten free diet

HD : Herpetiform dermatitis

HLA : Human leucocyte antigen

IEL : Intraepithelial lymphocytes

IET : Intraepithelial T-cells

MHC: Major histocompatibility complex

NCGS : Non-celiac gluten sensitivity

NICE : National Institute for Health and Care Excellence

PCD : Potential celiac disease

RCD : Refratory celiac disease

tTG : Anti-tissue transglutaminase antibody

T1D : Type 1 diabetes

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Introduction

Celiac disease (CD) is a systemic disease triggered by gluten ingestion, in genetically predisposed individuals. It manifests as an autoimmune enteropathy associated with specific circulating autoantibodies and human leucocyte antigen haplotype (HLA-DQ2 or HLA-DQ8). [1]

Aretaeus of Cappadocia, in 250 A.D., was the first to describe a chronic perturbation of "pepsis" (a.k.a. digestion) and "anadosis" (a.k.a. absorption) resulting in a general debility which was named "coeliac diathesis".[3, 4] The word "coeliac" derived from the Greek "koiliakos", which means abdominal.[71] However, it was only in 1888 that Samuel Gee published the first modern clinical detailed description of CD in the article "On the coeliac affection".[2] In 1908, in the United States, Christian Herter published a similar description, emphasizing the retardation in growth.[72] After these descriptions, CD was known as Gee-Herter's disease.[73]

The cause for this disease was unknown, although Gee had already linked it to diet. In twentieth century, several diets with positive results were advocated, such as banana diet proposed by Haas [74] and Fanconi's diet based on fruits and vegetables.[73] However, an association between grain consumption (wheat, rye, barley and, to a lesser extent, oat) was only described in the forties by the pediatrician Willem Dicke. This link came from the observation of the effect of food scarcity during the 2nd World War. Dicke observed that symptoms of children with CD improved when they were not eating bread or grains, and worsened after the war ended and these foods re-entered their diet.[73, 75]

Paulley, in 1954, described, detailed histological anomalies in the small intestine from surgical specimens (with chronic inflammation and atrophy in advanced cases) from patients with CD [76]. Histological assessment remains pivotal in the diagnosis of CD, till today.

In 1964, Berger first reported the presence of anti-gliadin antibodies (AGA) in a patient's blood.[77] It took up to 20 years to serology become a diagnostic criteria.[78, 79] More sensitive and specific serological tests, such as the anti-endomysium (EMA) [80] and anti-tissue transglutaminase antibodies (tTG), were identified since then.[81]

In 1972, Falchuk described the association between a specific HLA genotype and CD, and hypothesized that CD is a consequence of carrying an abnormal immune response

gene to gluten.[82] We know now that the presence of HLA-DQ2/8 is necessary (though not sufficient) to the development of CD, making HLA determination the third pillar in the diagnosis of CD. [31]

The first guidelines on CD were published in 1969 by the European Society for Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) and were last reviewed in 2019.[83, 84] The most recent guidelines on CD were published in 2013 and 2019 by the American College of Gastroenterology (ACG) and the European Society for the Study of Coeliac Disease (ESsCD), respectively.[46, 48]

This review aims to summarize the most recent evidence regarding pathophysiology, diagnosis and diagnostic challenges of CD.

Epidemiology

The prevalence of CD varies according to age, gender and region. A recent meta-analysis estimated a global prevalence of 1.4% by serological tests, and 0.7% by intestinal biopsy.[5] This is probably an underestimation of the real prevalence of CD, because it is estimated that only one in five patients with CD is diagnosed.[7] In this millennium, the prevalence of CD seems to have increased 33%, for unknown reasons, but probably associated with environmental factors. [5]

Women are 1.5 times more afflicted than men.[5] Also, the incidence of CD varies with age, being approximately 2 times more frequent in children than adults. However, there is a second peak on incidence of CD between 50-69 years.[85]

Genetics are a main conditioning in the risk for CD. In fact, there is an 80% concordance in homozygous twins.[86, 87] Besides HLA-DQ2/8 haplotype, over 40 other genetic loci were described as risk factors for CD.[88]

Environmental factors have been studied as risk factors for CD, such as age at gluten introduction, breastfeeding and infectious diseases.[9–11] Current recommendations stand for gluten introduction between 4 and 12 months of age,[89] however, an association with CD remains controversial. [12–14, 90, 91] Concerning breastfeeding, current literature does not suggest a benefit in preventing CD.[12, 14–17] Recurrent respiratory infections (in infants) and gastrointestinal infections (rotavirus and adenovirus in children and *Campylobacter* in adults) seem to associate with CD,[9, 10, 18] though evidence is weak.[19]

The amount and pattern of gluten consumption may have a role, and may account for the different prevalence of CD across Europe.[92]

Lastly, there are high-risk groups for CD including first degree relatives of CD patients [20] with prevalence up to 7.5% [93], patients with type 1 diabetes mellitus (T1D) [21] or other autoimmune diseases [22], IgA deficiency [23], and chromosomopathies such as Down syndrome [24] and Turner syndrome.[25] Interestingly, the proportion of CD patients in non-at-risk groups seems to be only 1:133, rising to 1:56 among symptomatic patients.[94]

Physiopathology

CD results from an intense immune response towards gluten, which leads to small bowel inflammation and destruction, with consequent malabsorption and autoimmune phenomena.[26]

Gluten consists of a group of proteins present in Gramineae of the tribe Triticiae, particularly wheat, rye and barley. Oats are phylogenetically more distant (tribe Aveneae), but share sufficient similarities so that some patients are also intolerant to it. Rice, maize, sorghum and millet are distant enough not to trigger CD.[95] Gluten is the Latin word for “glue” and it was named this way due to its viscoelastic and adhesive properties.[10] Even though gluten is widely used to refer to Gramineae disease-inducing proteins, strictly speaking, gluten specifically refers to protein from wheat, whereas secalins are present in rye and hordein in barley.[27] The wheat gluten contains two major protein components: monomeric water-soluble gliadins and multimeric water-insoluble glutenins.[28]

Gluten peptides are highly enriched in proline and glutamine. The high-proline content turns gluten resistant to cleavage by gastrointestinal proteases (which are deficient in prolyl endopeptidase activity), allowing the subsistence of polypeptides with up to 33 amino-acids.[29] This increases gluten’s pathogenic potential, since major histocompatibility complex (MHC) II molecules only presents peptides at least 9 amino-acids long.[30]

Gluten-peptides need to cross the epithelial barrier, since antigen-presenting cells (APC) that can recognize gluten reside mostly in the lamina propria. This can occur through several ways: via paracellular pathway, transcellular pathway or through dendritic cells

that cross the epithelial barrier. The paracellular pathway occurs through a damaged epithelium. Some peptides may interact with CXCR3 chemokine receptors inducing the release of zonulin, with subsequent disassembly of tight-junctions between enterocytes increasing the intestinal mucosa permeability to gluten. Transient intestinal infection (for example viral infection) or inflammation (for example drug induced, such as nonsteroidal anti-inflammatory drugs) may disrupt the epithelial barrier. In the transcellular pathway, gluten-secretory IgA complexes may bind to transferrin receptor CD71 that act as a transporter across the epithelial barrier.[8, 28, 31–33]

MHC-II molecules bind preferentially to peptides with negatively charged amino-acids. Proline-enriched gluten peptides have very few charged amino-acids. However, those peptides are highly susceptible to deamidation of glutamine residues to negatively-charged glutamate by tTG.[30] Deamidation significantly increases the stability of gluten-MHC complex, increasing their immunogenicity.[34]

Deamidated gluten peptides are presented by APC by binding to specific MHC class II antigen that map to HLA-DQ locus. That locus codifies antigen-presenting glycoproteins that are heterodimers constituted by a α-chain (encoded by allele DQA1) and a β-chain (encoded by allele DQB1). HLA-DQ2.5, DQ2.2, DQ8 (and probably DQ7.5 with very low affinity), and can bind to deamidated gluten-peptides, explaining why their presence is necessary, though not sufficient for development of CD. [96] In fact, these haplotypes are found in 40% of the general population and only 2 to 3% of them will develop the disease. [8] Nonetheless, about 90% of CD patients express HLA-DQ2.5 and roughly 10% HLA-DQ2.2 or HLA-DQ8. [35] Furthermore, there is a dose-effect for HLA-DQ2.5, since homozygous have a 5-fold increased risk for CD, as well as an increased risk for severe disease. [97] **(Table 1).**

HLA-DQ2.5 and HLA-DQ2.2 are similar, however, substitution of tyrosine in DQ2.5 for phenylalanine in DQ2.2, in residue DQα22, allows DQ2.5 to form a hydrogen-bond with gluten-peptide, increasing the stability of the HLA-DQ/gluten-peptide complex. Furthermore, HLA-DQ2.2 recognizes different peptides as HLA-DQ2.5, requiring a specific serine, threonine or aspartate residue in position P3, which are rare amino-acids in the gluten proteome. Consequently, HLA-DQ2.5 repertoire of recognizable peptides is higher. In fact, to date, 25 epitopes are known to be recognized by HLA-DQ2.5, whereas less than 10 by HLA-DQ2.2 and HLA-DQ8. [30]

Table 1. HLA and risk of CD

Haplotype	HLA alleles			Molecules			Risk of CD
	DQB1*	**DQA1***	**DRB1***	**β chain**	**α chain**		
DR3-DQ2	02:01	05:01	03	02:01	05:01	**cis DQ2.5**	High
DR5-DQ7	03:01	05:05	11/12	02:02	05:05	**trans DQ2.5**	
DR7-DQ2	02:02	02:01	07				
DR7-DQ2	02:02	02:01	07	02:02	02:01	**DQ2.2**	Low
DR5-DQ7	03:01	05:05	11/12	03:01	05:05	**DQ7.5**	Very low
DR4-DQ8	03:02	03	04	03:02	03	**DQ8**	Low

Adapted from Sollid LM, 2017 [96]

APC (dendritic-cells and macrophages) present the complex MHC-II-deamidated gliadin to CD4+ T-cells, which acquire a pro-inflammatory phenotype. The reason why CD4+ T-cells acquire an inflammatory rather than tolerant phenotype is unknown. Dendritic-cells may acquire an inflammatory phenotype (either by direct action of gluten or after other inflammatory stimuli) and release mediators (IL-15, IL-21, interferon-α) that turn CD4+ T-cells insensitive to the tolerogenic effect of transforming-growth factor-β and regulatory T-cells.[36]

Activated CD4+ T-cells promote differentiation of B-cells into plasma cells and release pro-inflammatory cytokines such interferon-γ and IL-21 that activate intraepithelial CD8+ T-cells (IET).[31, 35] IET acquire a cytotoxic NK-cell-like phenotype, damaging enterocytes. In fact, IL-15 upregulates IET expression of co-stimulatory NKG2D and CD94-NKG2C receptors, while upregulating their ligand (MICs and HLA-E) in enterocytes.[36] Activated CD4+ T-cells also secrete tumor necrosis factor-α, which acts on intestinal fibroblasts inducing their secretion of matrix metalloproteinases (contributing to mucosal destruction by dissolution of connective tissue) [37] and keratinocyte growth factor, an epithelial mitogen (contributing to crypt epithelial cells hyperplasia).[38] The innate immune system also has a role in mucosal destruction, with recruitment and activation of macrophages, neutrophils and eosinophils, through IET secretion of chemokines and arachidonic acid, and through direct activation of neutrophils by gliadin interaction with fMet-Leu-Phe receptor.[98]

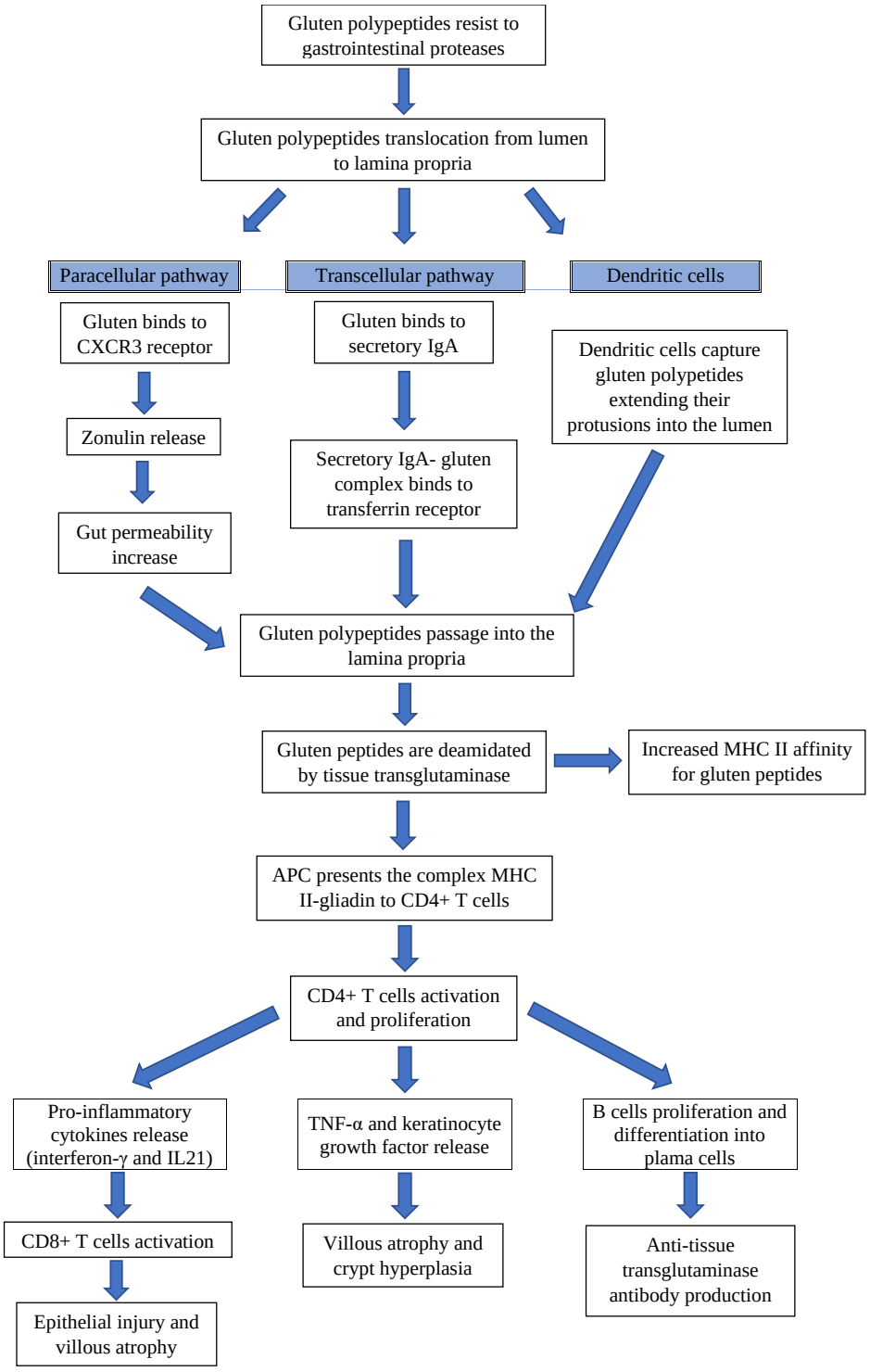

Figure 1. Schematic representation of the physiopathology

Lastly, transglutaminase-2-deamidated gluten complex may bind to receptors allowing internalization in specific B-cells, which then act as APC to CD4+ T-cells, further fuelling the immune response. Conversely, those B-cells may differentiate into plasma cells, explaining why specific anti-tTG antibody production only occurs under gluten-containing diet. [39] **(Figure 1).**

Definitions, clinical manifestations and associated diseases

Definitions

Most recent definitions on CD are shown in **Table 2**.

Table 2. Definitions

Classical celiac disease	Patient presents malabsorption signs and symptoms such as diarrhea, steatorrhea, weight loss and impaired growth. Formerly known as typical CD.[1] The usual presentation in children.[9]
Non-classical celiac disease	Formerly known as atypical CD, this is the most frequent form of the disease. Patient presents no malabsorption signs or symptoms, but with anaemia, chronic fatigue, osteoporosis, abdominal pain, abdominal distension, dermatitis herpetiformis among others.[1] The usual presentation in adults. [9]
Asymptomatic celiac disease	Patients do not present signs or symptoms associated to CD nor any improvement when on a gluten-free diet (GFD). These patients are often diagnosed through screening programs that target high-risk populations for CD. Patients present histological and serological changes. This term is preferred to silent CD.[1]
Potential celiac disease	Refers to patients that show positive serological tests, compatible HLA but normal intestinal biopsies. Patient may or may not show signs or symptoms and may or may not develop future enteropathy. [49, 57]

Clinical manifestations

The clinical spectrum of CD is wide, which accounts for a challenging diagnosis.

The classical gastrointestinal manifestations are chronic diarrhea (in 35%), abdominal pain (28%) and weight loss (22%).[8, 40] It can also present paradoxically with chronic constipation (20%), abdominal distension (20%), gastroesophageal reflux (12%) and even obesity.[8, 9] Classical manifestations are more common in children, whereas adults tend to be paucisymptomatic.[9]

The most common extra-intestinal manifestations are decreased bone mineralization (osteopenia in 50-70% and osteoporosis in 5.5%), anaemia (32%), arthralgia (29%),

fatigue (26%), and neurological symptoms (20%), particularly gluten ataxia and peripheral neuropathy.[8, 41] CD can also manifest with hypertransaminasemia (9-14%), recurrent aphthous stomatitis, tooth enamel defects, infertility, delayed puberty and short stature.[8, 41, 99] Most extra-intestinal manifestations improve with GFD, but early diagnosis is crucial and some manifestations may be irreversible such as enamel defects.[41]

CD associated diseases

CD associates with several genetic, autoimmune and neurological diseases.[31]

Concerning genetic disorders, prevalence of CD is higher in patients with chromosomopathies, being 5.5% in patients with Down syndrome, 6.5% with Turner syndrome, and 9.5% with Williams syndrome.[49] The reason for this increase is unknown but may be explained by a proinflammatory cytokine profile and impaired function of regulatory CD4+ T-cells associated to chromosomopathies.[25, 100]

Autoimmune glandular diseases, particularly T1D and thyroid disease, strongly associate with CD: 10-30% of CD patients have one of those two autoimmune diseases and up to 7% of patients with autoimmune glandular diseases have CD. T1D usually precedes CD.[9, 101] In fact, those conditions share a genetic background with a tight link between HLA-DQ2/8 and DR3/4.[101]

Herpetiform dermatitis (HD) is a dermatological autoimmune disease that also shares the genetic background with CD. Up to 20% of CD patients develop HD and more than 90% of HD patients have CD. HD diagnosis can be confirmed by skin biopsy demonstrating IgA deposits in the papillary dermis adjacent to the lesion. These patients present anti-tTG as well as IgA anti-epidermal transglutaminase antibodies. HD responds to GFD, although transient treatment with dapsone may be needed.[9, 41, 102]

CD patients have an increased risk for hepatic diseases such as steatosis, autoimmune hepatitis, primary biliary cholangitis (at least 20 fold increase)[103] and primary sclerosing cholangitis (4-8 fold increase).[104]

CD associates with several neurological disorders such as peripheral neuropathy (in up to 39%), cerebellar ataxia (in up to 6%), encephalopathy, and epilepsy. Gluten neuropathy is a sensitive neuropathy that associates with serological evidence of CD (even though histological enteropathy can only be demonstrated in one third of patients), which initially

affects hands and feet, but usually progresses. Mean age at diagnosis is 55 years. GFD can improve symptoms regardless of the presence or absence of enteropathy, however neuropathy may not reverse completely.[105] Gluten ataxia is an autoimmune injury of the cerebellum, induced by gluten ingestion, which manifests by typical serology, abnormal gait, muscle coordination, and fine control of voluntary movements, as well as cerebellum atrophy on magnetic resonance imaging (up to 60%). Mean age is 53 years old.[106] Studies on the effect of GFD are conflicting.[105, 107–109]

Finally, patients with selective IgA deficiency present a risk 10-20 times higher of CD.[110] The reverse is also true, IgA deficiency is 10-15 times more frequent in patients with CD.[111]

Diagnosis

Who to test?

All patients with signs, symptoms or laboratorial evidence of malabsorption should be tested for CD. Unexplained fatigue and recurrent mouth ulcers should also be investigated. Furthermore, patients with T1D or autoimmune thyroid disease should be regularly tested.[46, 48]

CD screening is recommended in patients with irritable bowel syndrome, since patients classified with irritable bowel syndrome (presenting with diarrhea or obstipation), are 4 times more likely of having CD than the general population.[112] Lastly, first-degree relatives CD patients should be screened, though there are no recommendations regarding the time interval for re-screening.[49]

The following high-risk groups should be considered for screening: children and adolescents with Down-, Turner-, Williams-Syndrome, patients with metabolic bone disorders, unexplained neurological symptoms, unexplained hypertransaminasemia or infertility, and dental enamel defects.[49] **(Table 3)**

Population based screening is not recommended, since it has not been proven that the diagnosis of asymptomatic patients improves their quality of life.[113, 114]

Table 3. Current recommendations on CD screening.

Offer serological testing	Consider serological testing
• Persistent unexplained abdominal or gastrointestinal symptoms • Faltering growth • Prolonged fatigue • Unexpected weight loss • Severe or persistent mouth ulcers • Unexplained iron, vitamin B12, or folate deficiency • Type 1 diabetes mellitus • Autoimmune thyroid disease • Irritable bowel syndrome • First degree relatives of CD patients	• Unexplained persistent raised liver enzymes • Metabolic bone disorder • Unexplained subfertility or recurrent miscarriage • Dental enamel defects • Unexplained neurologic symptoms • Down's syndrome • Turner's syndrome

Adapted from Downey L, et al. 2015 [42]

Diagnostic tools

CD diagnosis relies on 3 main pillars: serological tests, duodenal histology, and genetic testing. [43] **(Figure 2)**

Anti-tTG IgA is the recommended first-line serological test, being the most sensitive test (98%), with a very good specificity (96%).[26] Anti-tTG is determined through ELISA allowing quantitation. Anti-EMA IgA reacts to the same antigen of tTG, but tissue-bound, requiring immunofluorescence in tissue from primate's oesophagus or human umbilical cord. As such, it is more expensive, technically more challenging, operator-dependent, and only allowing qualitative results. [44] Anti-EMA IgA test is the most specific serological test [45] and should be used as a confirmatory test, especially when anti-tTG is lower than two times the upper limit of normal.[43, 46] Anti-tTG and anti-EMA IgG have low sensitivity, and should be interpreted carefully.[45]

AGA are not recommended for CD diagnosis due to their low sensitivity and specificity.[48, 115] The more recent anti-deamidated gliadin peptides (DGP), particularly IgG, which are superior to anti-DGP IgA and clearly superior to other IgG

antibodies, present 88% sensitivity and 99% specificity.[45] Anti-DGP IgG are particularly useful in patients with selective IgA deficiency. [46, 47]

Diagnosis in adults should start by measuring both anti-tTG IgA and IgA serum levels. If both positive, a positive duodenal biopsy confirms the diagnosis. If anti-tTG IgA is weakly positive and IgA serum levels are normal, anti-EMA IgA should be performed. Lastly, if there is IgA deficiency (IgA levels <7 mg/dL), IgG antibodies should be performed (particularly anti-DGP IgG).[44]

All serological tests should be performed in patients under regular gluten-containing diet, to avoid false negative results.[48] False positive results may occur with intestinal infections (for example *Giardia lamblia*) [116], chronic liver disease [117], congestive heart failure [118] and hypergammaglobulinemia.[119]

After the initial positive serological tests, all patients should undergo an upper endoscopy with duodenal biopsies.[49] These biopsies should also be performed in patients with negative serological tests, when clinical suspicion is high.[48]

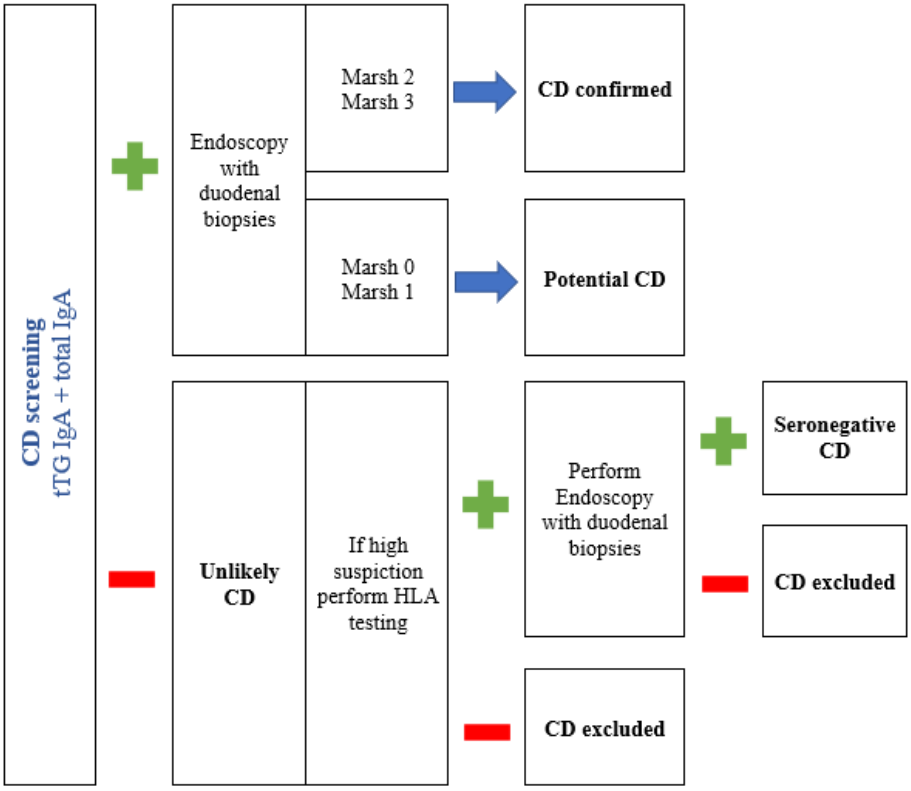

Figure 2. CD diagnosis flowchart

Genetic testing may have a role in the diagnosis of CD, particularly in excluding CD, since the absence of HLA-DQ2/8 has a negative predictive value of 100%. [53] This is particularly useful in seronegative patients, patients on a GFD who are unable/unwilling to undergo a gluten challenge or in those who refuse endoscopy.[47, 49, 115, 120]

Recently, an interesting study showed a positive predictive value of 100% with the triple combination of a positive genetic test, positive anti-EMA and a more than 10-fold increase in anti-tTG, which would allow the diagnosis in the absence of duodenal histology.[121]

Endoscopy findings have very low sensitivity, 11-22% for mucosal atrophy [122], even though some findings are very specific (up to 99%): scalloping duodenal folds, fissuring and mosaic pattern of the mucosa. [123, 124] Less specific findings are duodenal erosions, loss of folds, nodular mucosa and enhanced submucosal vessels. [124, 125] The role of advanced endoscopic techniques such as immersion endoscopy [126], NBI [127], iSCAN [128] and confocal [129] is still undetermined. [130] Capsule endoscopy is useful for patients who refuse to undergo traditional endoscopy or in case of complicated CD, such as refractory CD (RCD) type II, ulcerative jejunitis, adenocarcinoma and lymphoma. [131]

Histology is crucial for the diagnosis of CD in adults, and the way endoscopic biopsies are collected determine its accuracy. In fact, the distribution of lesions is discontinuous, and hence at least 4 duodenal biopsies should be collected. [48] Furthermore, 1 or 2 biopsies should be collected from the duodenal bulb (from 9 or 12 o'clock position), since it increases almost 10% the sensitivity in adults. [51] Bulb biopsies should be sent separately from more distal duodenal samples, because they should be interpreted carefully. Indeed, less than half bulb biopsies are high quality, because they can be hampered by the presence of Brunner glands and lymphoid tissue, peptic duodenitis and gastric metaplasia. Furthermore, villous are smaller in the bulb and can be misinterpreted as atrophic .[132, 133] Finally, biopsies should be collected one-bite at the time, avoiding double-bite biopsy specimen with each pass of the forceps, since this decreases the risk of losing specimens, increases 3-fold the chance of good orientation and minimizes the risk of tangential biopsies that overestimate mucosal atrophy.[134, 135] Duodenal biopsies should be performed under gluten containing diet to avoid false negatives.[44]

Histopathological findings characteristic of CD are increased number of IEL (≥40 IEL/100 enterocytes), crypt hyperplasia and villous atrophy.[44, 52] A normal histology should present <25 IEL/100 enterocytes being more numerous at the base of the villous and decreasing toward the top, and villous/crypt ratio should be higher than 3:1.[136] Histological abnormalities are classified according to the Marsh scale, modified by Oberhuber. **(Table 4)**

Table 4. Modified Marsh Classification

Marsh type	**Histological criterion (Marsh modified by Oberhuber)**		
	IEL > 40/100 enterocytes	Crypt hyperplasia	Villous atrophy
Type 0	no	no	no
Type 1	yes	no	no
Type 2	yes	yes	no
Type 3a	yes	yes	partial
Type 3b	yes	yes	subtotal
Type 3c	yes	yes	total

A positive serology associated with compatible histology (Marsh 2-3), confirms the CD diagnosis.[49, 50]

Several non-invasive markers are currently being evaluated to diagnose CD. Intestinal fatty acid binding protein (I-FABP) is a marker of enterocyte injury in CD. Patients with CD present higher serum levels compared to controls, which correlates with mucosal atrophy. I-FABP levels normalize after GFD in 80% of children, but not in adults. [137] Some studies also suggest a role of I-FABP in assessing adherence to GFD and accidental gluten ingestion. [138]

A promising technique is flow cytometry that recognize blood CD4+ T-cells that bind to HLA-DQ-gluten tetramers. Preliminar studies showed very good accuracy to differenciate CD patients from controls, even on GFD.[139, 140]

Diagnostic challenges

Seronegative CD patients present negative serology but positive histology and risk HLA, accounting for 2% of CD patients.[55, 56] To confirm a seronegative CD, patients should also improve of histology after GFD. However, GFD should only be advised after

excluding other diagnoses since seronegative CD accounts for only 30% of seronegative patients with villous atrophy or epithelial lymphocytosis.[44, 54, 141] Most patients with seronegative CD present with mild histology, usualy Marsh 1.[142] Furthermore, seronegative CD patients present more frequently the classic phenotype, even though they tend to be older when compared with seropositive CD patients (49 *versus* 36 years).[56] The physiopathology of seronegative CD is not yet clarified but some studies suggest that the high antibody-antigen affinity binding would entrap antibodies in the lamina propria away from the bloodstream, while others hypothesize immaturity of immune system as a possible cause of seronegativity.[143] Supporting the first theory, these patients may be identified with the presence of immunocomplexes with transglutaminase and anti-tTG in the mucosa by immunofluorescence.[144] Other explanations for seronegative CD are selective IgA deficiency, a diet poor in gluten, treatment with immunossupressors and refractory long-term CD.[141]

The differential diagnosis of seronegative CD are: autoimmune enteropathy (anti-enterocyte antibody positive), common variable immunodeficiency, Crohn's disease, eosinophilic gastroenteritis, infectious diseases (Whipple's disease, *Giardia* lamblia, tuberculosis, HIV-associated enteropathy, tropical sprue), bacterial overgrowth, lymphoproliferative diseases, drug-associated enteropathy, among others. [50, 145–147] Regarding drug-associated enteritis, the most frequent drugs are non-steroidal anti-inflammatory agents, immunomodulators and angiotensin-receptor antagonists, particularly olmesartan that is responsible for one fifth of seronegative duodenal atrophy findings in the US. [148] Non-CD mucosal atrophy reverts spontaneously, without GFD, in over two-third of patients. [141]

More difficult is the management of seronegative patients with IEL but without villous atrophy. IEL occurs in 5% of the population, of whom one third is due to CD. Suggests CD IEL being exclusively CD8+ T-cells without CD4+ T-cells, more than 5% of T-cells receptors being the type γ/δ, and loss of villous basal to apical IEL gradient.[44, 136, 149]

Potential CD (PCD) is another diagnostic challenge, which refers to seropositive patients with normal duodenal mucosa (Marsh 0) or IEL (Marsh 1) without crypt hyperplasia or villous atrophy. PCD account for 10% of CD patients, which may be asymptomatic, present gastrointestinal or extraintestinal manifestations[47] Whereas over 80% of children are asymptomatic [150, 151], the majority of adults (79%) with PCD are

symptomatic, mostly with a non-classic phenotype.[152] Symptomatic PCD patients should be kept on GFD, since it associates with clinical improvement. The management of asymptomatic PCD patients is less straightforward, since a recent prospective cohort study demonstrated a progression rate of PCD to overt CD of only 13% in 10 years. [153] Those patients should be kept on a gluten-containing diet and evaluated each 6 months for symptoms and serology, and perform duodenal biopsy every 2 years.[152]

Patients who initiated a GFD without prior CD diagnosis should be first tested for HLA since absence of HLA-DQ2/8 excludes CD. In the presence of HLA-DQ2/8, patients should repeat the diagnostic work-up after a gluten challenge.[154]

The classical gluten challenge consisted of consumption of 7.5 g/day of gluten for 6 to 8 weeks, however 3 g/day of gluten (equivalent to 2 slices of bread) is as effective. For patients who cannot tolerate a long gluten challenge, recent studies suggest that two weeks may be enough, performing serology and histology on the 4^{th} forth week.[154]

Differentiating between non-celiac gluten sensitivity (NCGS) and CD is another important issue. NCGS is 6 times more prevalent than CD [155] and is more frequent in females in their 2^{nd}-3^{rd} decade. [156] Clinical manifestations are similar to CDs, that is, diarrhea, abdominal distension, abdominal pain, among others, and elicited by gluten ingestion, in patients without CD or wheat allergy.[59] In NCGS, intestinal or extra-intestinal symptoms develop early (hours to days) after gluten ingestion and also resolve early (hours to days), after excluding gluten from diet. Conversely, in CD, both symptom appearance and disappearance take days to weeks after changes in diet gluten content. [58, 60] Unlike CD, NCGS does not associate autoimmune disorders. NCGS diagnosis is clinical since serology and histology are negative (60% Marsh 0 and 40% Marsh 1), and no biomarker has yet been identified.[61, 62] Diagnosis of NCGS requires exclusion of CD and wheat allergy (i.e. negative serum IgE antigens to wheat allergens and relevant skin prick tests) and confirmation by a clinical response to GFD, and recurrence of symptoms after gluten re-challenge.[59] The pathogenesis is unknown, but seems to be multifactorial resulting from an interplay between environment (including different components of wheat and other cereals, gluten and non gluten peptides), intestinal barrier dysfunction, gut dysbiota and immune-mediated abnormal responses, particularly innate imune responses.[156]

Treatment and follow up

A GFD is the only proven treatment for CD. This diet consists in a strict eviction of wheat and its gluten containing derivatives bulgur, couscous and seitan [43], rye, and barley.[63] Eviction of oat is not so straightforward. In fact, oats contain avenin, a peptid that is similar to gluten and that may elicit a similar immune reaction. Furthermore, oats can induce symptoms as a reaction to an increase in fiber content. As such, gluten-free oat consumption should be restricted to 50-60g/day, patients should be clinically and serologically monitored and oats should be avoided in patients with severe disease.[157]

The amount of gluten patients can tolerate varies. As little as $1/100^{th}$ of a slice of bread (equivalent to 50 mg of gluten) is sufficient to induce mucosal atrophy. Gluten-free is defined as less than 20 ppm of gluten, the equivalent of 6 mg/day. Less than 10 mg/day seems to be safe.[158, 159]

Due to social and economic constraints or misconceptions concerning GFD, strict adherence to GFD is low, ranging between 17% and 48%.[64, 65] This is of major importance, since mortality seems to increase 5-fold in patients who do not adhere to GFD.[66] An experienced dietician should check for diet compliance regularly.[160]

After starting a GFD, symptoms such as diarrhea, abdominal distension and abdominal pain improve after one month and usually disappear after 6 months.[67] GFD can decrease the risk or improve extra-intestinal manifestations and CD-related conditions. It partially corrects osteopenia, but bone mass seldom returns to normal values.[161]

Most patients become seronegative after 6 months of GFD and only 17% of patients show positive serological tests after 1 year [68, 69], which suggests gluten contamination.[49] The preferred serological test in the follow-up on GFD is IgA tTG.[70]

Histological normalization takes longer, particularly in adults, in whom it takes 2 to 5 years. [70] A recent study suggested that only 66% of patients who strictly complied to GFD showed total histological recovery after 1 year, which is in contrast with children in whom histological recovery can be expected in 95%.[162]

In addition to classical CD, non-classical CD, seronegative CD, symptomatic PCD, and patients with HD or gluten ataxia also benefit from a GFD. [47] GFD is not recommended for asymptomatic adults with PCD, since only a minority of these patients will develop villous atrophy.[152]

GFD should always be lifelong, even if the patient acquires clinical tolerance to gluten. In fact, about 20% of patients maintain histological remission after gluten reintroduction. However, histological remission is not a true latency, since those patients tend to present positive serology and IEL, as well as an increased risk for extra-intestinal manifestations and potential for a late relapse.[163]

Several alternative and complementary therapeutics are currently being studied but none showed consistent enough results to be advised in clinical practice. Investigational drugs address different mechanisms of the pathogenesis and include genetically modified less immunogenic wheat strains, prolyl-endopeptidases, non-absorbable polymers with high affinity for gliadin, drugs that decrease intercellular space of enterocytes, drugs that hamper gluten deamination, HLA inhibitor agents, among others.[164]

Patients should be monitored in the first 6 months and then yearly for clinical manifestations, adherence to diet, serology, nutrition and development of associated conditions such as osteoporosis and autoimmune thyroid disease. Laboratorial tests should include anti-tTG IgA, screening for micronutrients deficiency such as full blood count, iron, folic acid, vitamin B12, calcium and vitamin D. Thyroid function and anti-thyroid antibodies may also be considered. [10, 70] Follow-up endoscopy is not routinely advised and should be restricted to patients with persistent or relapsing symptoms despite proper diet. [48] Bone mass should be assessed every 1-2 years in all patients older than 20 years.[43] Lastly, vaccination against pneumococci, *Haemophilus influenza* and meningococci are strongly recommended.[49]

Complications

RCD occurs in approximately 1.5% of CD cases, and is defined as the persistence of malabsorption signs, symptoms and villous atrophy in patients on GFD for at least a year, when no other causes for villous atrophy or malignancy were identified. [50] The main cause of persistent villous atrophy is inadvertent ingestion of gluten. Other causes should be excluded: lactose intolerance, irritable bowel syndrome, small bowel bacterial overgrowth, pancreatic insufficiency and microscopic colitis.[46]

RCD can be further subclassify in two variants, type I and II, on the bases of phenotype and clonality of IEL. Type I RCD characterizes by normal IEL with polyclonality of the T-cell receptor, whereas type II present aberrant T-cells that lack surface CD8 and CD3 expression, while expressing intracytoplasmatic CD3 and monoclonal T-cell receptor

rearrangement. The distinction of these two entities is crucial because treatment and prognosis is different. [43, 165, 166] Type I RCD usually responds to steroids and budesonide or immunomodulators such as azathioprine. Type II RCD is more aggressive, and associates with ulcerative jejunoileitis, severe malabsorption, and high risk of progression to EATL (enteropathy-associated T-cell lymphoma) in 50% of the cases, in 5-10 years [161, 167], with a 5-year survival rate of 44-58%. [161, 166] Type II RCD does not respond to steroids and may require treatment with cladribine or autologous/allogenic bone marrow transplant. Targeting IL-15 is a promising therapeutic strategy.[168]

Patients with CD, especially long-standing and untreated patients, present a higher risk of developing EATL and small intestine adenocarcinoma, when compared to general population. Five-year survival rate for EATL is 11%. The risk for developing other malignancies is still an unanswered topic.[43, 169–171]

Conclusion

CD was described for the first time almost two thousand years ago, however it remains a clinical challenge.

CD presents a wide range of unspecific signs and symptoms, both gastrointestinal and extra-intestinal. Adults tend to be paucisymptomatic, presenting non-classical symptoms, making the diagnosis more difficult. Physicians should use an active case finding strategy, screening patients with suggestive clinical manifestations and those who belong to high-risk groups.

The diagnosis requires highly accurate serological tests and duodenal biopsy with a compatible histopathology. The presence of HLA-DQ2/8 is mandatory for the development of CD and is particularly helpful in uncertain diagnosis. Typical histology findings such as villous atrophy and crypt hyperplasia, are unspecific, which explains the necessity of the other two diagnostic pillars.

The treatment options are scarce being lifelong GFD the only proven treatment for CD, though intense research for different treatment strategies.

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References

1. Ludvigsson JF, Leffler DA, Bai JC, et al (2013) The Oslo definitions for coeliac disease and related terms. Gut 62:43–52
2. Gee S (1888) On the coeilac affection. St Bartholemews Hosp Rep 24, 17
3. Gasbarrini GB, Mangiola F, Gerardi V, et al (2014) Coeliac disease: An old or a new disease? History of a pathology. Intern Emerg Med 9:249–256
4. Dowd B, Walker-Smith J (1974) Samuel Gee, Aretaeus, and the Coeliac Affection. Br Med J 2:442
5. Singh P, Arora A, Strand TA, et al (2018) Global Prevalence of Celiac Disease: Systematic Review and Meta-analysis. Clin Gastroenterol Hepatol 16:823-836.e2
6. Mustalahti K, Catassi C, Reunanen A, et al (2010) The prevalence of celiac disease in Europe: Results of a centralized, international mass screening project. Ann Med 42:587–595
7. Lionetti E, Gatti S, Pulvirenti A, et al (2015) Celiac disease from a global perspective. Best Pract Res Clin Gastroenterol 29:365–379
8. Leonard MM, Sapone A, Catassi C, et al (2017) Celiac disease and nonceliac gluten sensitivity: A review. JAMA - J Am Med Assoc 318:647–656

9. McAllister BP, Williams E, Clarke K (2018) A Comprehensive Review of Celiac Disease/Gluten-Sensitive Enteropathies. Clin Rev Allergy Immunol 1–18

10. Lebwohl B, Sanders DS, Green PHR (2018) Coeliac disease. Lancet 391:70–81

11. Dias JA (2017) Celiac Disease: What Do We Know in 2017? GE Port J Gastroenterol 24:275–278

12. Vriezinga SL, Auricchio R, Bravi E, et al (2014) Randomized feeding intervention in infants at high risk for celiac disease. N Engl J Med 371:1304–1315

13. Aronsson CA, Lee HS, Liu E, et al (2015) Age at gluten introduction and risk of celiac disease. Pediatrics 135:239–245

14. Lionetti E, Castellaneta S, Francavilla R, et al (2014) Introduction of gluten, HLA status, and the risk of celiac disease in children. N Engl J Med 371:1295–1303

15. Szajewska H, Shamir R, Chmielewska A, et al (2015) Systematic review with meta-analysis: Early infant feeding and coeliac disease-update 2015. Aliment Pharmacol Ther 41:1038–1054

16. Szajewska H, Shamir R, Mearin L, et al (2016) Gluten introduction and the risk of coeliac disease: A position paper by the european society for pediatric gastroenterology, hepatology, and nutrition. J Pediatr Gastroenterol Nutr 62:507–513

17. Mearin ML (2015) The prevention of coeliac disease. Best Pract Res Clin Gastroenterol 29:493–501

18. Stene LC, Honeyman MC, Hoffenberg EJ, et al (2006) Rotavirus infection frequency and risk of celiac disease autoimmunity in early childhood: A longitudinal study. Am J Gastroenterol 101:2333–2340

19. Ludvigsson JF, Murray JA (2019) Epidemiology of Celiac Disease. Gastroenterol Clin North Am 48:1–18

20. Nellikkal SS, Hafed Y, Larson JJ, et al (2019) High Prevalence of Celiac Disease Among Screened First-Degree Relatives. Mayo Clin Proc 94:1807–1813

21. Pham-Short A, Donaghue KC, Ambler G, et al (2015) Screening for celiac disease in type 1 diabetes: A systematic review. Pediatrics 136:e170–e176

22. Elli L, Bonura A, Garavaglia D, et al (2012) Immunological comorbity in coeliac disease: Associations, risk factors and clinical implications. J Clin Immunol 32:984–990

23. Meini A, Pillan NM, Villanacci V, et al (1996) Prevalence and diagnosis of celiac disease in IgA-deficient children. Ann Allergy, Asthma Immunol 77:333–336

24. Carnicer J, Farré C, Varea V, et al (2001) Prevalence of coeliac disease in Down's syndrome. 263–267

25. Marild K, Størdal K, Hagman A, et al (2016) Turner syndrome and celiac disease: A case-control study. Pediatrics 137:

26. Guandalini S, Assiri A (2014) Celiac disease: A review. JAMA Pediatr 168:272–278

27. Kagnoff MF (2005) Overview and pathogenesis of celiac disease. Gastroenterology 128:10–18

28. Balakireva A V., Zamyatnin AA (2016) Properties of gluten intolerance: Gluten structure, evolution, pathogenicity and detoxification capabilities. Nutrients 8:

29. Shan L, Molberg Ø, Parrot I, et al (2002) Structural basis for gluten intolerance in Celiac Sprue. Science (80-) 297:2275–2279

30. Stamnaes J, Sollid LM (2015) Celiac disease: Autoimmunity in response to food antigen. Semin Immunol 27:343–352

31. Parzanese I, Qehajaj D, Patrinicola F, et al (2017) Celiac disease: From pathophysiology to treatment. World J Gastrointest Pathophysiol 8:27

32. Lammers KM, Lu R, Brownley J, et al (2008) Gliadin Induces an Increase in Intestinal Permeability and Zonulin Release by Binding to the Chemokine Receptor CXCR3. Gastroenterology 135:194–204

33. Rescigno M, Sabatino A Di (2009) Dendritic cells in intestinal homeostasis and disease. Clin Invest 119:2441–2450

34. Xia J, Sollid LM, Khosla C (2005) Equilibrium and kinetic analysis of the unusual binding behavior of a highly immunogenic gluten peptide to HLA-DQ2. Biochemistry 44:4442–4449

35. Du Pré MF, Sollid LM (2015) T-cell and B-cell immunity in celiac disease. Best Pract Res Clin Gastroenterol 29:413–423

36. Jabri B, Sollid LM (2009) Tissue-mediated control of immunopathology in coeliac disease. Nat Rev Immunol 9:858–870

37. Pender SL, Tickle SP, Docherty AJ, et al (1997) A major role for matrix metalloproteinases in T cell injury in the gut. J Immunol 158:1582–90

38. Bajaj-Elliott M, Poulsom R, Pender SLF, et al (1998) Interactions between stromal cell-derived keratinocyte growth factor and epithelial transforming growth factor in immune-mediated crypt cell hyperplasia. J Clin Invest 102:1473–1480

39. Sollid LM, Molberg, Mcadam S, et al (1997) Autoantibodies in coeliac disease: Tissue transglutaminase guilt by association? Gut 41:851–852

40. Fernández A, González L, de-la-Fuente J (2010) Coeliac disease: Clinical features in adult populations. Rev Esp Enfermedades Dig 102:466–471

41. Laurikka P, Nurminen S, Kivelä L, et al (2018) Extraintestinal manifestations of celiac disease: Early detection for better long-term outcomes. Nutrients 10:1–14

42. Downey L, Houten R, Murch S, et al (2015) Recognition, assessment, and management of coeliac disease: Summary of updated NICE guidance. BMJ 351:1–5

43. Elli L, Ferretti F, Orlando S, et al (2018) Management of celiac disease in daily clinical practice. Eur J Intern Med 61:15–24

44. Kowalski K, Mulak A, Jasiñska M, et al (2017) Diagnostic challenges in celiac disease. Adv Clin Exp Med 26:729–737

45. Schyum AC, Rumessen JJ (2013) Serological testing for celiac disease in adults. United Eur Gastroenterol J 1:319–325

46. Al-Toma A, Volta U, Auricchio R, et al (2019) European Society for the Study of Coeliac Disease (ESsCD) guideline for coeliac disease and other gluten-related disorders. United Eur Gastroenterol J 7:583–613

47. Lau MSY, Sanders DS (2017) Optimizing the diagnosis of celiac disease. Curr Opin Gastroenterol 33:173–180

48. Rubio-Tapia A, Hill ID, Kelly CP, et al (2013) ACG clinical guidelines: Diagnosis and management of celiac disease. Am J Gastroenterol 108:656–676

49. Husby S, Koletzko S, Korponay-Szabó IR, et al (2012) European society for pediatric gastroenterology, hepatology, and nutrition guidelines for the diagnosis of coeliac disease. J Pediatr Gastroenterol Nutr 54:136–160

50. Ludvigsson JF, Bai JC, Biagi F, et al (2014) Diagnosis and management of adult coeliac disease: Guidelines from the British society of gastroenterology. Gut 63:1210–1228

51. McCarty T, O'Brien C, Gremida A, et al (2018) Efficacy of duodenal bulb biopsy for diagnosis of celiac disease: a systematic review and meta-analysis. Endosc Int Open 06:E1369–E1378

52. Oberhuber G (2000) Histopathology of celiac disease. Biomed Pharmacother 54:368–372

53. Sollid LM, Lie BA (2005) Celiac disease genetics: Current concepts and practical applications. Clin Gastroenterol Hepatol 3:843–851

54. Schiepatti A, Sanders DS, Biagi F (2018) Seronegative coeliac disease: Clearing the diagnostic dilemma. Curr Opin Gastroenterol 34:154–158

55. Schiepatti A, Biagi F, Fraternale G, et al (2017) Short article: Mortality and differential diagnoses of villous atrophy without coeliac antibodies. Eur J Gastroenterol Hepatol 29:572–576

56. Volta U, Caio G, Boschetti E, et al (2016) Seronegative celiac disease: Shedding light on an obscure clinical entity. Dig Liver Dis 48:1018–1022

57. Trovato CM, Montuori M, Valitutti F, et al (2019) The Challenge of Treatment in Potential Celiac Disease. Gastroenterol Res Pract 2019:1–6

58. Volta U, Caio G, De Giorgio R, et al (2015) Non-celiac gluten sensitivity: A work-in-progress entity in the spectrum of wheat-related disorders. Best Pract Res Clin Gastroenterol 29:477–491

59. Catassi C, Elli L, Bonaz B, et al (2015) Diagnosis of non-celiac gluten sensitivity (NCGS): The salerno experts' criteria. Nutrients 7:4966–4977

60. Schuppan D, Pickert G, Ashfaq-Khan M, et al (2015) Non-celiac wheat sensitivity: Differential diagnosis, triggers and implications. Best Pract Res Clin Gastroenterol 29:469–476

61. Volta U, Tovoli F, Cicola R, et al (2012) Serological tests in gluten sensitivity (nonceliac gluten intolerance). J Clin Gastroenterol 46:680–685

62. Mansueto P, Seidita A, D'Alcamo A, et al (2014) Non-Celiac Gluten Sensitivity: Literature Review. J Am Coll Nutr 33:39–54

63. Bascuñán KA, Vespa MC, Araya M (2017) Celiac disease: understanding the gluten-free diet. Eur J Nutr 56:449–459

64. Leffler DA, Edwards-George J, Dennis M, et al (2008) Factors that influence adherence to a gluten-free diet in adults with celiac disease. Dig Dis Sci 53:1573–1581

65. Hall NJ, Rubin G, Charnock A (2009) Systematic review: Adherence to a gluten-free diet in adult patients with coeliac disease. Aliment Pharmacol Ther 30:315–330

66. Corrao G, Corazza GR, Bagnardi V, et al (2001) Mortality in patients with coeliac disease and their relatives: a cohort study. 358:356–361

67. Oxentenko AS, Murray JA (2015) Celiac Disease: Ten Things That Every Gastroenterologist Should Know. Clin. Gastroenterol. Hepatol. 13:

68. Zanini B, Lanzarotto F, Mora A, et al (2010) Five year time course of celiac disease serology during gluten free diet: Results of a community based " CD-Watch" program. Dig Liver Dis 42:865–870

69. Rashid M, Lee J (2016) Serologic testing in celiac disease Practical guide for clinicians. Can Fam Physician 62:38–43

70. Mulder CJ, Wierdsma NJ, Berkenpas M, et al (2015) Preventing complications in celiac disease: Our experience with managing adult celiac disease. Best Pract Res Clin Gastroenterol 29:459–468

71. Freeman HJ (2015) Celiac disease: A disorder emerging from antiquity, its evolving classification and risk, and potential new treatment paradigms. Gut Liver

9:28–37

72. Herter CA (1909) On Infantilism from Chronic Intestinal Infection, characterized by the Overgrowth and Persistence of Flora of the Nursling Period. Bost Med Surg J 160:416

73. Yan D, Holt PR (2009) Willem Dicke. Brilliant clinical observer and translational investigator. discoverer of the toxic cause of celiac disease. Clin Transl Sci 2:446–448

74. Haas SV (1924) The value of the banana in the treatment of coeliac disease. Am J Dis Child 24:421–437

75. Van Berge-Henegouwen GP, Mulder CJJ (1993) Pioneer in the gluten free diet: Willem-Karel Dicke 1905-1962, over 50 years of gluten free diet. Gut 34:1473–1475

76. Paulley JW (1954) Observations on the aetiology of idiopathic steatorrhoea: Jejunal and lymph-node biopsies. Br Med J 2:1318–1325

77. Berger E, Burgin-Wolff A, Freudenberg E (1964) Diagnostisehe Bewertung des Nachweises yon Gliadin-AntikSrpern bei Ciiliakie Von. 788–790

78. Kilander AF, Dotevall G, Fällström SP, et al (1983) Evaluation of gliadin antibodies for detection of coeliac disease. Scand J Gastroenterol 18:377–383

79. Signer E, Bürgin-Wolff A, Berger R, et al (1979) Antibodies to gliadin as a screening test for coeliac disease. A prospective study. Helv Paediatr Acta 34:41–52

80. Chorzelski TP, Beutner EH, Sulej J, et al (1984) IgA anti-endomysium antibody. A new immunological marker of dermatitis herpetiformis and coeliac disease. Br J Dermatol 111:395–402

81. Dieterich W, Ehnis T, Bauer M, et al (1997) Identification of tissue transglutaminase as the autoantigen of celiac disease. Nat Med 4:303–308

82. Falchuk ZM, Rogentine GN, Strober W (1972) Predominance of histocompatibility antigen HLA-8 in patients with gluten-sensitive enteropathy. J Clin Invest 51:1602–1605

83. Wagener P (2007) A Brief History of Celiac Disease. Univ Chicago Celiac Dis Cent 7:1–4

84. Husby S, Koletzko S, Korponay-Szabó I, et al (2020) European Society Paediatric Gastroenterology, Hepatology and Nutrition Guidelines for Diagnosing Coeliac Disease 2020. J Pediatr Gastroenterol Nutr 70:141–156

85. West J, Fleming KM, Tata LJ, et al (2014) Incidence and prevalence of celiac disease and dermatitis herpetiformis in the UK over two decades: Population-based study. Am J Gastroenterol 109:757–768

86. Greco L, Romino R, Coto I, et al (2002) The first large population based twin study of coeliac disease. Gut 50:624–628

87. Nisticò L, Fagnani C, Coto I, et al (2006) Concordance, disease progression, and heritability of coeliac disease in Italian twins. Gut 55:803–804

88. Withoff S, Li Y, Jonkers I, et al (2016) Understanding Celiac Disease by Genomics. Trends Genet 32:295–308

89. Fewtrell M, Bronsky J, Campoy C, et al (2017) Complementary feeding: A position paper by the European Society for Paediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) committee on nutrition. J Pediatr Gastroenterol Nutr 64:119–132

90. Silano M, Agostoni C, Sanz Y, et al (2016) Infant feeding and risk of developing celiac disease: A systematic review. BMJ Open 6:

91. Pinto-Sánchez MI, Verdu EF, Liu E, et al (2016) Gluten Introduction to Infant Feeding and Risk of Celiac Disease: Systematic Review and Meta-Analysis. J Pediatr 168:132-143.e3

92. Weile B, Cavell B, Nivenius K, et al (1995) Striking Differences in the Incidence of Childhood Celiac Disease Between Denmark and Sweden. J Pediatr Gastroenterol Nutr 21(1):64–68

93. Singh P, Arora S, Lal S, et al (2015) Risk of celiac disease in the first- and second-degree relatives of patients with celiac disease: A systematic review and meta-analysis. Am J Gastroenterol 110:1539–1548

94. Fasano A, Berti I, Gerarduzzi T, et al (2003) Prevalence of Celiac Disease in At-Risk and Not-At-Risk Groups in the United States. Arch. Intern. Med. 163:

95. Kagnoff MF (2007) Celiac disease : pathogenesis of a model immunogenetic disease. J Clin Invest 117:41–49

96. Sollid LM (2017) The roles of MHC class II genes and post-translational modification in celiac disease. Immunogenetics 69:605–616

97. Karinen H, Kärkkäinen P, Pihlajamäki J, et al (2006) Gene dose effect of the DQB1*0201 allele contributes to severity of coeliac disease. Scand J Gastroenterol 41:191–199

98. Caio G, Volta U, Sapone A, et al (2019) Celiac disease: A comprehensive current review. BMC Med 17:1–20

99. Reunala T, Salmi TT, Hervonen K, et al (2018) Dermatitis herpetiformis: A common extraintestinal manifestation of coeliac disease. Nutrients 10:1–9

100. Pellegrini FP, Marinoni M, Frangione V, et al (2012) Down syndrome, autoimmunity and T regulatory cells. Clin Exp Immunol 169:238–243

101. Kahaly GJ, Frommer L, Schuppan D (2018) Celiac disease and endocrine autoimmunity – the genetic link. Autoimmun Rev 17:1169–1175

102. Rodrigues F, Bachmeyer C (2018) Coeliac disease and dermatitis herpetiformis. Lancet 392:916

103. Sørensen HT, Thulstrup AM, Blomqvist P, et al (1999) Risk of primary biliary liver cirrhosis in patients with coeliac disease: Danish and Swedish cohort data. Gut 44:736–738

104. Ludvigsson JF, Elfström P, BroomÉ U, et al (2007) Celiac Disease and Risk of Liver Disease: A General Population-Based Study. Clin Gastroenterol Hepatol 5:63–69

105. Mearns ES, Taylor A, Thomas Craig KJ, et al (2019) Neurological manifestations of neuropathy and ataxia in celiac disease: A systematic review. Nutrients 11:380

106. Hadjivassiliou M, Sanders DD, Aeschlimann DP (2015) Gluten-related disorders: Gluten ataxia. Dig Dis 33:264–268

107. Bushara KO (2005) Neurologic presentation of celiac disease. Gastroenterology 128:92–97

108. Freeman HJ (2008) Neurological disorders in adult celiac disease. Can J Gastroenterol 22:909–911

109. Hadjivassiliou M, Rao DG, Grìnewald RA, et al (2016) Neurological dysfunction in coeliac disease and non-coeliac gluten sensitivity. Am J Gastroenterol 111:561–567

110. Korponay-Szabó IR, Dahlbom I, Laurila K, et al (2003) Elevation of IgG antibodies against tissue transglutaminase as a diagnostic tool for coeliac disease in selective IgA deficiency. Gut 52:1567–1571

111. Kumar V, Jarzabek-Chorzelska M, Sulej J, et al (2002) Celiac disease and immunoglobulin A deficiency: How effective are the serological methods of diagnosis? Clin Diagn Lab Immunol 9:1295–1300

112. Irvine AJ, Chey WD, Ford AC (2017) Screening for Celiac Disease in Irritable Bowel Syndrome: An Updated Systematic Review and Meta-analysis. Am J Gastroenterol 112:65–76

113. Ludvigsson JF, Card TR, Kaukinen K, et al (2015) Screening for celiac disease in the general population and in high-risk groups. United Eur Gastroenterol J 3:106–120

114. Leffler DA, Kelly CP (2014) The Cost of a Loaf of Bread in Symptomless Celiac Disease. Gastroenterology 147:557–559

115. Korponay-Szabó IR, Troncone R, Discepolo V (2015) Adaptive diagnosis of coeliac disease. Best Pract Res Clin Gastroenterol 29:381–398

116. Hanevik K, Wik E, Langeland N, et al (2018) Transient elevation of anti-transglutaminase and anti-endomysium antibodies in Giardia infection. Scand J Gastroenterol 53:809–812

117. Vecchi M, Folli C, Donato MF, et al (2003) High rate of positive anti-tissue transglutaminase antibodies in chronic liver disease: Role of liver decompensation and of the antigen source. Scand J Gastroenterol 38:50–54

118. Peracchi M, Trovato C, Longhi M, et al (2002) Tissue transglutaminase antibodies in patients with end-stage heart failure. Am J Gastroenterol 97:2850–2854

119. Castillo NE, Theethira TG, Leffler DA (2015) The present and the future in the diagnosis and management of celiac disease. Gastroenterol Rep 3:3–11

120. Sciurti M, Fornaroli F, Gaiani F, et al (2018) Genetic susceptibilty and celiac disease: What role do HLA haplotypes play? Acta Biomed 89:17–21

121. Fuchs V, Kurppa K, Huhtala H, et al (2019) Serology-based criteria for adult coeliac disease have excellent accuracy across the range of pre-test probabilities. Aliment Pharmacol Ther 49:277–284

122. Emani MH, Karimi S, Nemati A (2008) Do endoscopic markers still play a role in diagnosis of celiac disease? Indian J Gastroenterol 27:183–185

123. Ianiro G, Gasbarrini A, Cammarota G (2013) Endoscopic tools for the diagnosis and evaluation of celiac disease. World J Gastroenterol 19:8562–8570

124. Dickey W (2006) Endoscopic markers for celiac disease. Nat Clin Pract Gastroenterol Hepatol 3:546–551

125. Balaban D V., Popp A, Vasilescu F, et al (2015) Diagnostic yield of endoscopic markers for celiac disease. J Med Life 8:452–457

126. Cammarota G, Pirozzi GA, Martino A, et al (2004) Reliability of the "immersion technique" during routine upper endoscopy for detection of abnormalities of duodenal villi in patients with dyspepsia. Gastrointest Endosc 60:223–228

127. Dutta AK, Sajith KG, Shah G, et al (2014) Duodenal villous morphology assessed using magnification narrow band imaging correlates well with histology in patients with suspected malabsorption syndrome. Dig Endosc 26:720–725

128. Cammarota G, Ianiro G, Sparano L, et al (2013) Image-enhanced endoscopy with i-scan technology for the evaluation of duodenal villous patterns. Dig Dis Sci 58:1287–1292

129. Leong RWL, Nguyen NQ, Meredith CG, et al (2008) In Vivo Confocal Endomicroscopy in the Diagnosis and Evaluation of Celiac Disease. Gastroenterology 135:1870–1876

130. Penny HA, Mooney PD, Burden M, et al (2016) High definition endoscopy with or without I-Scan increases the detection of celiac disease during routine endoscopy. Dig Liver Dis 48:644–649

131. Lewis SK, Semrad CE (2019) Capsule Endoscopy and Enteroscopy in Celiac Disease. Gastroenterol Clin North Am 48:73–84

132. Taavela J, Popp A, Korponay-Szabo IR, et al (2016) A Prospective Study on the Usefulness of Duodenal Bulb Biopsies in Celiac Disease Diagnosis in Children: Urging Caution. Am J Gastroenterol 111:124–133

133. Voutilainen M, Juhola M, Färkkilä M, et al (2003) Gastric metaplasia and chronic inflammation at the duodenal bulb mucosa. Dig Liver Dis 35:94–98

134. Padda S, Shah I, Ramirez FC (2003) Adequacy of mucosal sampling with the "two-bite" forceps technique: A prospective, randomized, blinded study. Gastrointest Endosc 57:170–173

135. Latorre M, Lagana SM, Freedberg DE, et al (2015) Endoscopic biopsy technique in the diagnosis of celiac disease: One bite or two? Gastrointest Endosc 81:1228–1233

136. Brown I, Mino-Kenudson M, Deshpande V, et al (2006) Intraepithelial lymphocytosis in architecturally preserved proximal small intestinal mucosa: An increasing diagnostic problem with a wide differential diagnosis. Arch Pathol Lab Med 130:1020–1025

137. Adriaanse MPM, Tack GJ, Passos VL, et al (2013) Serum I-FABP as marker for enterocyte damage in coeliac disease and its relation to villous atrophy and circulating autoantibodies. Aliment Pharmacol Ther 37:482–490

138. Adriaanse MPM, Leffler DA, Kelly CP, et al (2016) Serum I-FABP Detects Gluten Responsiveness in Adult Celiac Disease Patients on a Short-Term Gluten Challenge. Am J Gastroenterol 111:1014–1022

139. Sarna VK, Lundin KEA, Mørkrid L, et al (2018) HLA-DQ–Gluten Tetramer Blood Test Accurately Identifies Patients With and Without Celiac Disease in Absence of Gluten Consumption. Gastroenterology 154:886-896.e6

140. Sarna VK, Skodje GI, Reims HM, et al (2018) HLA-DQ:gluten tetramer test in

blood gives better detection of coeliac patients than biopsy after 14-day gluten challenge. Gut 67:1606–1613

141. Aziz I, Peerally MF, Barnes JH, et al (2017) The clinical and phenotypical assessment of seronegative villous atrophy; A prospective UK centre experience evaluating 200 adult cases over a 15-year period (2000-2015). Gut 66:1563–1572

142. Dore MP, Pes GM, Dettori I, et al (2017) Clinical and genetic profile of patients with seronegative coeliac disease: The natural history and response to gluten-free diet. BMJ Open Gastroenterol 4:1–8

143. Ierardi E, Losurdo G, Piscitelli D, et al (2015) Seronegative celiac disease: Where is the specific setting? Gastroenterol Hepatol from Bed to Bench 8:110–116

144. Salmi TT, Collin P, Korponay-Szabó IR, et al (2006) Endomysial antibody-negative coeliac disease: Clinical characteristics and intestinal autoantibody deposits. Gut 55:1746–1753

145. Elli L, Branchi F, Sidhu R, et al (2017) Small bowel villous atrophy: celiac disease and beyond. Expert Rev Gastroenterol Hepatol 11:125–138

146. Jansson-Knodell CL, Hujoel IA, Rubio-Tapia A, et al (2018) Not All That Flattens Villi Is Celiac Disease: A Review of Enteropathies. Mayo Clin Proc 93:509–517

147. Kamboj AK, Oxentenko AS (2017) Clinical and Histologic Mimickers of Celiac Disease. Clin Transl Gastroenterol 8:e114

148. Degaetani M, Tennyson CA, Lebwohl B, et al (2013) Villous atrophy and negative celiac serology: A diagnostic and therapeutic dilemma. Am J Gastroenterol 108:647–653

149. Walker MM, Murray JA, Ronkainen J, et al (2010) Detection of celiac disease and lymphocytic enteropathy by parallel serology and histopathology in a population-based study. Gastroenterology 139:112–119

150. Auricchio R, Tosco A, Piccolo E, et al (2014) Potential celiac children: 9-year follow-up on a gluten-containing diet. Am J Gastroenterol 109:913–921

151. Tosco A, Salvati VM, Auricchio R, et al (2011) Natural History of Potential Celiac Disease in Children. Clin Gastroenterol Hepatol 9:320–325

152. Volta U, Caio G, Giancola F, et al (2016) Features and Progression of Potential Celiac Disease in Adults. Clin Gastroenterol Hepatol 14:686-693.e1

153. Lionetti E, Castellaneta S, Francavilla R, et al (2019) Long-Term Outcome of Potential Celiac Disease in Genetically at-Risk Children: The Prospective CELIPREV Cohort Study. J Clin Med 8:186

154. Leffler D, Schuppan D, Pallav K, et al (2013) Kinetics of the histological, serological and symptomatic responses to gluten challenge in adults with coeliac disease. Gut 62:996–1004

155. Sapone A, Bai JC, Ciacci C, et al (2012) Spectrum of gluten-related disorders: Consensus on new nomenclature and classification. BMC Med 10:13

156. Volta U, De Giorgio R, Caio G, et al (2019) Nonceliac Wheat Sensitivity: An Immune-Mediated Condition with Systemic Manifestations. Gastroenterol Clin North Am 48:165–182

157. Dennis M, Lee AR, McCarthy T (2019) Nutritional Considerations of the Gluten-Free Diet. Gastroenterol Clin North Am 48:53–72

158. Hischenhuber C, Crevel R, Jarry B, et al (2006) Review article: Safe amounts of gluten for patients with wheat allergy or coeliac disease. Aliment Pharmacol Ther 23:559–575

159. Akobeng AK, Thomas AG (2008) Systematic review: Tolerable amount of gluten for people with coeliac disease. Aliment Pharmacol Ther 27:1044–1052

160. Simpson S, Thompson T (2012) Nutrition Assessment in Celiac Disease. Gastrointest Endosc Clin N Am 22:797–809

161. Malamut G, Cellier C (2015) Complications of coeliac disease. Best Pract Res Clin Gastroenterol 29:451–458

162. Galli G, Esposito G, Lahner E, et al (2014) Histological recovery and gluten-free diet adherence: A prospective 1-year follow-up study of adult patients with coeliac disease. Aliment Pharmacol Ther 40:639–647

163. Matysiak-Budnik T, Malamut G, De Serre NPM, et al (2007) Long-term follow-up of 61 coeliac patients diagnosed in childhood: Evolution toward latency is

possible on a normal diet. Gut 56:1379–1386

164. Costes LMM, Meresse B, Cerf-Bensussan N, et al (2015) The role of animal models in unravelling therapeutic targets in coeliac disease. Best Pract Res Clin Gastroenterol 29:437–450

165. Roshan B, Leffler DA, Jamma S, et al (2011) The incidence and clinical spectrum of refractory celiac disease in a north american referral center. Am J Gastroenterol 106:923–928

166. Malamut G, Cellier C (2015) Refractory celiac disease: Epidemiology and clinical manifestations. Dig Dis 33:221–226

167. Nijeboer P, van Wanrooij RLJ, van Gils T, et al (2017) Lymphoma development and survival in refractory coeliac disease type II: Histological response as prognostic factor. United Eur Gastroenterol J 5:208–217

168. Malamut G, Cellier C (2019) Refractory Celiac Disease. Gastroenterol Clin North Am 48:137–144

169. Tio M, Cox MR, Eslick GD (2012) Meta-analysis: Coeliac disease and the risk of all-cause mortality, any malignancy and lymphoid malignancy. Aliment Pharmacol Ther 35:540–551

170. Ilus T, Kaukinen K, Virta LJ, et al (2014) Incidence of malignancies in diagnosed celiac patients: a population-based estimate. Am J Gastroenterol 109:1471–1477

171. Catassi C, Bearzi I, Holmes GKT (2005) Association of celiac disease and intestinal lymphomas and other cancers. Gastroenterology 128:79–86