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Guidelines

Guidelines of the Italian societies of gastroenterology on the diagnosis and management of coeliac disease and dermatitis herpetiformis ☆,☆☆

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ABSTRACT

Introduction: Coeliac disease and dermatitis herpetiformis are immune-mediated diseases triggered by the consumption of gluten in genetically predisposed individuals. These guidelines were developed to provide general practitioners, paediatricians, gastroenterologists, and other clinicians with an overview on the diagnosis, management and follow-up of coeliac patients and those with dermatitis herpetiformis.
Methods: Guidelines were developed by the Italian Societies of Gastroenterology. Following a systematic literature review, the Grading of Recommendations Assessment, Development and Evaluation methodology was used to assess the certainty of the evidence. Statements and recommendations were developed by working groups consisting of gastroenterologists and a paediatrician with expertise in this field.
Results: These guidelines provide a practical guidance for the diagnosis, management and follow-up of coeliac patients and dermatitis herpetiformis in children and adults, both in primary care and in specialist settings. We developed four sections on diagnosis, gluten-free diet, follow-up and risk of complications in adults, one section focused on diagnosis and follow-up in children and one on the diagnosis and management of dermatitis herpetiformis.
Conclusions: These guidelines may support clinicians to improve the diagnosis and management of patients with coeliac disease.

1. Introduction

Coeliac disease (CeD) is an immune-mediated enteropathy triggered by the consumption of gluten in genetically predisposed individuals [1]. Potential CeD, seronegative CeD and refractory/complicated CeD are subtypes of CeD which have been identified with specific clinical, serologic and histologic features. Dermatitis herpetiformis (DH) is an autoimmune disease of the skin caused by the ingestion of gluten which is frequently associated with CeD. It manifests with extremely itchy clusters of vesicular lesions on erythematous skin with a symmetric distribution [2]. Other conditions associated with the consumption of gluten or wheat include wheat allergy, gluten ataxia and non-coeliac gluten sensitivity.

Gluten refers to a group of water-insoluble proteins present in various cereals including wheat (and related species such as spelt, emmer, einkorn and Khorasan), barley and rye. Gluten is

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responsible for the viscosity, elasticity, resistance and cohesive properties of dough which are important in leavening. Oats are another gluten-containing cereal which will be discussed separately in the section on following a gluten-free diet (GFD) as it is a special case. Gluten can be isolated from dough by washing it thoroughly with water until its water-soluble components such as starch, albumins and globulins are removed, leaving a sticky substance composed of water-insoluble proteins (gliadins and glutenins) which are together referred to as gluten.

The prevalence of CeD has increased significantly over time, similarly to most other immune-mediated diseases [3,4]. This increase in prevalence is related to improvements in diagnostic testing for CeD, but also due to the identification of groups of patients at high risk of developing CeD [5]. It has been recently suggested that a relationship may exist between the simultaneous reduction in overall infant mortality and the increase in prevalence of CeD which has occurred over the past 30–40 years [6]. It should be noted, however, that the majority of patients with CeD remain undiagnosed.

In western countries the prevalence of CeD is estimated to be around 0.6% considering only diagnoses confirmed by duodenal biopsy, while it rises to 1.0% in serologic screening studies of the general population. Females are affected more often than males although the exact ratio varies from study to study. CeD is diagnosed amongst all age groups at least 70% of diagnoses are made after 20 years of age [7,8]. In these cases, CeD may have developed in adulthood or may have developed in childhood but the diagnosis was missed until adulthood [4].

Both environmental and genetic factors are related to the development of gluten-related diseases. The role of HLA-DQA1 and HLA-DQB1 in the presentation of gluten peptides to the immune system makes it the most important genetic risk factor for the development of CeD [9,10].

Some environmental/lifestyle factors, other than exposure to gluten, may also have a role in the development of CeD, or in the onset of symptoms, but they have not yet led to primary prevention strategies [11]. Recent studies have instead shown no relationship between the development of CeD and breastfeeding or timing of gluten introduction into the diet [12,13]. The quantity of gluten ingested in the first 3 years of life has instead been found to be relevant in the development of CeD [14–17].

These guidelines were developed to provide general practitioners, paediatricians, gastroenterologists, and other clinicians with an overview on the diagnosis, management and follow-up of coeliac patients and dermatitis herpetiformis.

2. Materials and methods

The Italian Society of Gastroenterology and Endoscopy (SIGE) have proposed these guidelines to which three other Italian Societies, the Italian Association of Hospital Gastroenterologists and Digestive Endoscopists (AIGO), Italian Society of Digestive Endoscopy (SIED) and Italian Society of Gastroenterology, Hepatology and Pediatric Nutrition (SIGENP) have adhered and, therefore, they are the result of a collaborative work. The entire group consisted of six gastroenterologists and one paediatrician with particular expertise in CeD. At a first online meeting in March 2020 the research group identified 13 clinical questions to answer, using the patient, intervention, control and outcome (PICO) process (Supplementary 1). A systematic review of the literature was carried out for each research question using MEDLINE (accessed via PubMed), EMBASE electronic databases and the Cochrane Database of Systematic Reviews (Cochrane Library) from January 1985 to January 2022, including meta-analyses, observational studies and randomised trials written in English, and periodically updated. Furthermore, the most recently published guidelines on CeD were reviewed, discussed and evaluated on how they answered the chosen PICO questions [18–20]. The working group followed the GRADE methodology (https://www.gradeworkinggroup.org/) to assess the quality of evidence for statements/recommendations, and classified the recommendations into four categories: strong recommendation for an intervention *(implying it should be done)*, conditional recommendation for an intervention *(implying it should probably be done)*, conditional recommendation against an intervention *(implying it should probably not be done)* and strong recommendation against an intervention *(implying it should not be done)*. The level of evidence was classified in four categories: high, moderate, low or very low quality, based on a strict assessment of the quality of evidence in the literature on each topic. The recommendations were also based on other factors, such as desirable and undesirable consequences of alternative management strategies, variability in values and preferences and the use of resources (costs).

Each component of the research group worked on specific PICO questions: two rounds of voting were held to verify the overall degree of agreement on the recommendations developed by each member of the research group. Two final meetings were then held to produce the final manuscript. The manuscript was then revised by two internal reviewers (AC, GPI). Table 1 summarizes these guidelines' statements, grade of recommendation and levels of evidence.

3. Results and recommendations

Section 1. Coeliac Disease Diagnosis

Statement 1.1: Coeliac disease should be excluded in adults with classical or non-classical symptoms/signs or belonging to high-risk groups.

Strong recommendation, high quality evidence

CeD may present with very heterogeneous clinical pictures. The classical presentation is characterised by malabsorptive signs and symptoms which include diarrhoea, steatorrhea, weight loss, or growth retardation in children [21–23]. However, CeD may present with many other non-classical signs and symptoms, such as anaemia, irritable-bowel syndrome-like manifestations, neuropathy, ataxia, osteoporosis and bone fracture, unexplained liver enzyme abnormalities, spontaneous abortions and other gynaecological manifestations [24–32]. There are also some cases in which patients do not present any signs or symptoms of the disease (asymptomatic CeD). Nevertheless, despite the lack of symptoms, in some of these cases beginning a GFD leads to an improvement of patients' general well-being (subclinical CeD) [1]. Malabsorption in CeD, if present, is due to damage to the small bowel mucosa leading to loss of absorptive surface area and reduction of digestive enzymes), leading to reduced absorption of micronutrients such as fat-soluble vitamins, iron, vitamin B12 and folate [33]. Proactive case-finding using serologic testing in individuals with mild/atypical symptoms or in high-risk groups is probably the best strategy currently available to increase diagnoses [34]. The risk of CeD is significantly increased amongst those with a first-degree and also second-degree family history for CeD [35–37].

Amongst patients at a high-risk of CeD there are those with associated autoimmune conditions. Hashimoto's thyroiditis is one of the most common associated conditions [38]. It has been reported to be three times more frequent in coeliac patients than in the general population [39], while 2.7% of patients with autoimmune thyroiditis are affected by CeD [40]. Other associated autoimmune conditions include type 1 diabetes, which coexists with CeD in 8% of cases [41], psoriasis and other skin disorders [42], autoimmune atrophic gastritis [43] and autoimmune hepatitis [44].

Table 2 lists situations in which patients should be tested for CeD.

Table 1
All statements with level of evidence, grade of recommendation and agreement.

		Recommendation	Quality of evidence
Section 1. Coeliac Disease diagnosis			
Statement 1.1:	Coeliac disease should be excluded in adults with classical or non-classical symptoms/signs or belonging to high-risk groups.	Strong	High
Statement 1.2:	When coeliac disease is suspected, at any age, IgA anti-tissue transglutaminase 2 antibodies should be tested.	Strong	High
Statement 1.3	IgA endomysial antibodies are suggested as a confirmatory test when low titre IgA anti-tissue transglutaminase 2 antibodies are found.	Conditional	Moderate
Statement 1.4	Total IgA should be measured to exclude IgA deficiency at the time of serologic testing for coeliac disease. In patients with total selective IgA deficiency, diagnosis and follow-up serologic testing should be based on IgG antibodies (IgG anti-deamidated gliadin peptide antibodies and IgG anti-transglutaminase antibodies).	Strong	Moderate
Statement 1.5	When coeliac disease is suspected, all serologic tests and duodenal biopsies should be performed while patients are on a gluten containing diet.	Strong	High
Statement 1.6	Duodenal biopsy should be performed in adults with suspected coeliac disease and positive coeliac-specific antibodies.	Strong	High
Statement 1.7	HLA typing for DQ2/DQ8 should not be routinely performed when coeliac disease is suspected.	Strong	Moderate
Statement 1.8	Capsule endoscopy should not be performed for diagnosis of coeliac disease, except for rare cases when upper GI endoscopy cannot be performed, while it may be used to exclude complications of coeliac disease.	Strong	Moderate
Statement 1.9	Diagnosis of coeliac disease should be based on clinical manifestations, serology and duodenal histology. Positive coeliac-specific antibodies and villous atrophy confirm the diagnosis of coeliac disease.	Strong	High
Statement 1.10	Potential coeliac disease should be diagnosed when serology is positive (both IgA anti-tTG and EMA), confirmed at a dedicated laboratory, villous atrophy is absent (reviewed by an expert pathologist) and HLA typing is compatible. The decision to start a gluten-free diet should be taken with the patient and mainly depends on the presence or absence of signs and/or symptoms of disease.	Conditional	Low
Statement 1.11	An increased IEL count in the absence of villous atrophy on duodenal biopsy (Marsh 1) is not specific for coeliac disease. Marsh 1 with negative serology is not suggestive of CeD.	Strong	Moderate
Statement 1.12	Seronegative coeliac disease should be diagnosed only once other causes of villous atrophy have been excluded. Coeliac specific antibodies, both IgA and IgG, must be negative, HLA typing must be compatible and response to a gluten-free diet after one year must be verified.	Strong	Moderate
Statement 1.13	When patients with suspected coeliac disease are already on a gluten-free diet, gluten challenge is recommended before diagnostic testing for coeliac disease.	Strong	Moderate
Section 2 Gluten-free diet			
Statement 2.1	Patients diagnosed with coeliac disease should start a strict, lifelong gluten-free diet.	Strong	High
Statement 2.2	Dietary instruction by an expert dietitian, particularly during the initial period when starting a gluten-free diet, is suggested for patients diagnosed with coeliac disease.	Conditional	Very low
Statement 2.3	Testing forironand vitamin D is recommended in patients diagnosed with coeliac disease.	Strong	High
Statement 2.4	Following a nutritionally balanced gluten-free diet is recommended for patients diagnosed with coeliac disease.	Strong	High
Section 3. Follow-up			
Statement 3.1	A combined evaluation of symptoms, laboratory tests, and serology during follow-up is recommended in all patients with coeliac disease.	Strong	Moderate
Statement 3.2	A follow-up duodenal biopsy should be performed in patients with coeliac disease who have persistent symptoms or laboratory test abnormalities while on a gluten free diet.	Strong	Moderate
Statement 3.3	Serological screening for coeliac disease is recommended in first-degree family members of coeliac patients. Those with positive serology, or who have symptoms suggestive of coeliac disease, should undergo duodenal biopsy.	Strong	Moderate
Statement 3.4	Pneumococcal vaccination is suggested in patients diagnosed with coeliac disease, particularly if comorbidities are present.	Conditional	Moderate
Statement 3.5	Patients diagnosed with coeliac disease who have signs or symptoms of malabsorption, DEXA is recommended at time of diagnosis. All other coeliac patients should be screened for low bone mineral density with DEXA by 30–35 years of age.	Strong	Moderate
Statement 3.6	DEXA should be performed every 2–3 years in coeliac patients with low bone mineral density, poor gluten-free diet adherence or persistence of villous atrophy. Coeliac patients with normal bone mineral density should repeat DEXA every 5 years.	Strong	Moderate
Statement 3.7	Evaluating coeliac patients for psychological disorders at diagnosis and during follow-up is suggested and counselling should be provided when required.	Strong	Moderate
Section 4. Coeliac disease complications			
Statement 4.1	Assuming the initial diagnosis of coeliac disease is certain and other possible causes have been excluded, refractory coeliac disease or other complications should be suspected in patients with persistent or recurrent signs or symptoms of malabsorption despite being on a gluten-free diet for at least one year.	Strong	Moderate
Statement 4.2	Patients with suspected refractory coeliac disease should be referred urgently to a specialized tertiary centre. Prednisone/budesonide is recommended as initial treatment.	Strong	Moderate

(*continued on next page*)

Table 1 (*continued*)

		Recommendation	Quality of evidence
Section 5. Coeliac disease diagnosis and follow-up in children			
Statement 5.1	In children with suspected coeliac disease the ESPGHAN criteria should be followed, avoiding duodenal biopsy in those with high IgA anti-tissue transglutaminase antibody titres (>10x upper limit of normality) and positive IgA endomysial antibodies. In all other children (anti-tissue transglutaminase antibody titres<10x or discrepant serology) duodenal biopsy should be performed.	Strong	High
Statement 5.2	Children diagnosed with coeliac disease should start a gluten-free diet only once the diagnosis is certain.	Strong	High
Statement 5.3	Adolescents with coeliac disease should gradually transit to adult gastroenterologist care. Transition should be managed with the patient and should include a written report on how the paediatric diagnosis of coeliac disease was made and clinical data on follow-up.	Strong	Moderate
Section 6. Dermatitis Herpetiformis			
Statement 6.1	Direct immunofluorescence on perilesional skin biopsy is recommended in patients with suspected dermatitis herpetiformis. Detection of granular IgA deposits in the dermal papillae confirms the diagnosis.	Strong	Moderate
Statement 6.2	Coeliac-specific antibodies and duodenal biopsy are recommended in patients diagnosed with dermatitis herpetiformis to verify the presence of concomitant coeliac disease.	Strong	Moderate
Statement 6.3	Patients diagnosed with dermatitis herpetiformis should start a strict life-long gluten-free diet.	Strong	High

Table 2
Situations in which testing for coeliac disease should be performed.

Presence of signs and symptoms suggestive of CeD	Chronic diarrhoea
	Unexplained weight loss
	Iron-deficiency anaemia
	Deficiency of iron, folate or vitamin B12
	Growth retardation in children
	Constipation in children
	Irritable bowel syndrome-like symptoms
	Chronic abdominal pain
	Nausea or recurrent vomiting
	Recurrent aphthous stomatitis / dental enamel defects
	Unexplained liver enzyme abnormalities
	Unexplained amylase/pancreatic enzyme abnormalities
Presence of conditions associated with CeD	First (Second) - degree family history of CeD
	Dermatitis herpetiformis
	Hashimoto's thyroiditis and Graves disease
	Type 1 Diabetes mellitus
	Psoriasis or other skin disorders
	Other autoimmune diseases (e.g. autoimmune atrophic gastritis, autoimmune hepatitis, primary biliary cholangitis, Sjögren syndrome)
	Microscopic colitis
	Down syndrome, Turner syndrome, Williams syndrome
	IgA deficiency
	Osteopenia and osteoporosis
	Unexplained ataxia or peripheral neuropathy
	Epilepsy
	Infertility, recurrent spontaneous abortions, delayed menarche, premature menopause
	Chronic fatigue syndrome, fibromyalgia
	Hyposplenism or functional asplenia
	Pulmonary hemosiderosis
	IgA nephropathy
	If CeD is highly suspected, duodenal biopsy should be performed even if serology is negative

CeD: Coeliac Disease.

Another unusual and very rare scenario is that of "coeliac crisis", of which only 42 cases have been described in 29 papers published over 50 years. It is characterised by an acute onset of gastrointestinal symptoms which rapidly worsen, requiring hospitalisation and parenteral nutrition. In the majority of cases, it has been described as the onset of CeD, but in some cases it has been described in patients with an established diagnosis of CeD who did not follow a strict GFD [45]. Although the causes of such an aggressive onset are unclear, in about half of these patients, a triggering event such as gastrointestinal infections, surgical procedures, or pregnancy occurred within a few months prior to onset [46].

These patients present severe dehydration with significant complications such haemodynamic instability, acute kidney injury, metabolic acidosis and electrolyte abnormalities. Weight loss, anaemia, hypoalbuminaemia, and other nutritional deficiencies may also be present. Patients with such a clinical picture need to be hospitalised for rehydration, correction of electrolyte abnormalities, and initiation of a GFD. In some cases, total parenteral nutrition and/or systemic glucocorticoid therapy may be necessary [47].

Statement 1.2: When coeliac disease is suspected, at any age, IgA anti-tissue transglutaminase antibodies 2 should be tested.

Strong recommendation, high quality evidence

Statement 1.3: IgA endomysial antibodies are suggested as a confirmatory test when low titre IgA anti-tissue transglutaminase 2 antibodies are found.

Conditional recommendation, moderate quality evidence

After the development of anti-gliadin antibodies (AGA), now obsolete due to their low diagnostic accuracy for CeD, several other antibody tests were developed, including anti-reticulin antibodies,

IgA endomysial antibodies (EmA) and, finally, IgA anti-tissue transglutaminase 2 antibodies (normally known as anti-transglutaminase antibodies, IgA anti-tTG). The identification of tissue transglutaminase 2 (tTG2) as the target antigen of EmA was an important discovery [48]. A recent meta-analysis has described a sensitivity and specificity of IgA anti-tTG of 90.7% (95% confidence interval: 87.3%, 93.2%) and 87.4% (84.4%, 90.0%) in adults and 97.7% (91.0%, 99.4%) and 70.2% (39.3%, 89.6%) in children; and of IgA EmA of 88.0% (75.2%, 94.7%) and 99.6% (92.3%, 100%) in adults and 94.5% (88.9%, 97.3%) and 93.8% (85.2%, 97.5%) in children [49].

The lower specificity of anti-tTG might be related to the possibility of finding low-titre positive IgA anti-tTG antibodies, which are present in other conditions such as hypergammaglobulinaemia, autoimmune diseases, chronic liver disease, congestive heart failure, and gastroenteritis [50]. Therefore, IgA anti-tTG testing can be considered as a first step, and EmA can be used as a confirmatory test, particularly when the IgA anti-tTG titres are low (<2 times the upper limit of normality).

Statement 1.4: Total IgA should be measured to exclude IgA deficiency at the time of serologic testing for coeliac disease. In patients with total selective IgA deficiency, diagnosis and follow-up serologic testing should be based on IgG antibodies (IgG anti-deamidated gliadin peptide antibodies and IgG anti-transglutaminase antibodies).

Strong recommendation, moderate quality evidence

It should be noted that 2–3% of coeliac patients is affected by IgA deficiency. It is therefore important that total IgA is measured at time of serologic testing to exclude IgA deficiency [51]. When IgA deficiency is present IgG anti-deamidated gliadin peptide antibodies (IgG anti-DGP) and/or IgG anti-tissue transglutaminase antibodies (IgG anti-tTG) should be tested [52,53].

Deamidated gliadin peptides (DGPs) bind with high affinity to HLA-DQ2 or DQ8 expressed by antigen presenting cells and induce a strong inflammatory T cell response in the small bowel mucosa of CeD patients [54]. Anti-DGP antibodies have a higher specificity for CeD in comparison to AGAs. An isolated positivity of IgA and/or IgG anti-DGP antibodies in patients at low risk of CeD is predictive of CeD only in 15% of cases, with the remaining cases being false positives [55].

Alongside traditional serology, point-of-care tests, particularly on capillary blood and saliva, are being studied for the diagnosis of CeD. The results of point-of-care tests in adults are currently lacking in consistency and have therefore not seen widespread use in clinical practice, although their use could be a cost-effective strategy to bridge the diagnostic gap of adult CeD in primary care [56–60].

Statement 1.5: When coeliac disease is suspected, all serologic tests and duodenal biopsies should be performed while patients are on a gluten containing diet.

Strong recommendation, high quality evidence

It is extremely important that serologic testing for CeD is performed while on a gluten containing diet. The presence of antibodies targeting gliadin, DGPs, and tTG2 all depend on the ingestion of gluten. A reduction in intake or complete exclusion of gluten from the diet leads to a reduction in antibodies directed against gliadin and tTG2. A weakly positive antibody titre may become negative within only a few weeks from the start of a strict GFD [61]. After 6–12 months of adherence to a GFD, 80% of patients have negative serology, and after 5 years, this occurs in over 90% of patients [62].

Statement 1.6: Duodenal biopsy should be performed in adults with suspected coeliac disease and positive coeliac-specific antibodies.

Strong recommendation, high level of evidence

The key endoscopic features of CeD are mucosal fissures, mucosal nodularity, duodenal bulb atrophy with visible submucosal vessels and loss of, reduction, or scalloping of the circular folds of Kerckring. These features have a high specificity for CeD and for other forms of non-coeliac villous atrophy [63]. It is, however, very important to note that in approximately a third of cases the endoscopic picture is completely normal at time of diagnosis of CeD. Therefore, if CeD is suspected on a clinical/serological basis, duodenal biopsies should be obtained even if the duodenum appears normal from an endoscopic point of view [64]. There are some upper GI endoscopic techniques which may lead to improvements in the diagnosis of CeD, but these are currently limited due to availability, required expertise, tolerability and costs [65].

Lesions in CeD may be discontinuous and may involve areas of the duodenum with a varying degree of severity [66]. Multiple biopsies (at least four) should always be obtained from the second or third part of the duodenum if CeD is suspected [67]. Obtaining biopsies of the duodenal bulb may increase diagnostic accuracy, as in some cases the enteropathy may be limited to these regions [68], especially in clinical forms of moderate severity in which no signs of malnutrition are present [69]. Each duodenal specimen should be obtained using a single-biopsy technique and correctly orientated, to permit a better evaluation of villous architecture [70], preferably on Millipore cellulose acetate filters. Histopathological evaluation is based on the application of standardised classifications. In 1992 Marsh proposed a system for grading the severity of histological changes in CeD, to facilitate the identification of the lesions in CeD [71]. Subsequently, Rostami and later Oberhuber proposed a standardised report based on the Marsh classification, in which stage 3 is subdivided into 3A, 3B, and 3C, which are respectively characterised by mild, moderate and severe villous atrophy [72,73].

This modified Marsh classification is used by the majority of histopathologists both for the diagnosis and follow-up, allowing for an evaluation of histologic recovery after initiation of a GFD, even if Marsh himself has questioned the subdivision of stage 3 lesions [74]. Finally, Corazza and Villanacci proposed a simpler classification, with the aim of increasing inter-observer reproducibility and facilitating the comparison of biopsies obtained throughout follow-up [75].

Histopathologic evaluation of small bowel biopsies should be performed on correctly orientated biopsy samples containing 3–4 consecutive villi-crypt units. The normal ratio between villous height and crypt depth varies from 3:1 to 5:1 in the second part of the duodenum, while a ratio of 2:1 is considered normal in the duodenal bulb [76]. The presence of sporadic intraepithelial lymphocytes (IEL) is considered normal. They are more prevalent on the lateral aspect of villi, decreasing in number from the base to apex of the villi [77]. A count of over 25 IEL/100 epithelial cells is instead considered abnormally increased [78].

Table 3 summarises the essential points a histopathologic report should cover. Considering the large variability in the clinical manifestations of CeD and various histopathological features which may be confused with CeD, communication between histopathologists and gastroenterologists is vital.

Statement 1.7: HLA typing for DQ2/DQ8 should not be routinely performed when coeliac disease is suspected.

Strong recommendation, moderate quality evidence

The vast majority of CeD patients (90–95%) express the DQ2 heterodimer encoded by the DQA1*05 and DQB1*02 alleles. The

Table 3
Essential points to address in a histopathology report.

1. The overall number of biopsies obtained in the second part of the duodenum, and in the duodenal bulb
2. Whether biopsies are adequately orientated or not
3. The percentage of IELs (using CD3 immunohistochemistry when there is doubt)
4. Villous architecture (normal, partial, subtotal, or total atrophy). Presence of crypt hyperplasia, ratio of villous height to crypt depth
5. Description of the lamina propria: an infiltrate of lymphocytes, plasma cells, eosinophils, and occasionally neutrophils is present in CeD
6. The presence of Brunner's glands
7. A summary of findings using a standardised classification such as the modified Marsh classification or/and the Corazza-Villanacci classification

IEL: Intraepithelial lymphocyte; CeD: Coeliac disease.

presence of HLA molecules predisposing to CeD is necessary for CeD to develop, but as their prevalence in the general population is 30–40%, they have no role in establishing a diagnosis of CeD [79].

The DQA1*05 and DQB1*02 alleles may be present on the same chromosome (*cis* configuration) or on different chromosomes (trans configuration). In both cases this leads to the expression of the HLA DQ2.5 molecule [80,81]. Patients with CeD who do not have HLA DQ2.5 generally express HLA DQ8, encoded by the DQA1*0301 and DQB1*0302 alleles. In the very few cases lacking both DQ2.5 and DQ8, DQ2.2 is expressed, encoded by DQA1*0201 and DQB1*0202. Finally, even more rarely, it is possible for CeD patients to have none of the aforementioned HLA molecules, in which case the HLA DQ7.5 molecule is present, encoded by the DQA1*0505 and DQB1*0301 alleles [10,80,81]. Negative testing for HLA DQ2 and DQ8 makes a diagnosis of CeD very unlikely, with a negative predictive value of more than 99% [82].

Testing for HLA-DQ2/DQ8 should therefore be used to exclude CeD in certain situations, including:

a) when the results of coeliac-specific serology and of histology are in disagreement: absence of villous atrophy with positive IgA anti-tTG and EmA, or villous atrophy with negative serology;
b) evaluation of patients placed on a GFD before testing for CeD was performed;
c) in first-degree family members if excluding a genetic predisposition to CeD is desired.

Statement 1.8: Capsule endoscopy should not be performed for diagnosis of coeliac disease, except for rare cases when upper GI endoscopy cannot be performed, while it may be used to exclude complications of coeliac disease.

Strong recommendation, moderate quality evidence

A meta-analysis showed that VCE has a sensitivity of 89% and a specificity of 95% for diagnosis of CeD [83]. VCE may be used in patients who cannot undergo upper GI endoscopy, as it has a good level of agreement with histopathology [84]. The sensitivity of VCE is lower in cases of partial villous atrophy and for lesions without villous atrophy (Marsh 1–2) [85]. VCE may be useful to identify complications of CeD [86], and it may also be necessary to perform an enteroscopy, especially amongst patients with a suspicion of lymphoma, adenocarcinoma or ulcerative jejunoileitis [87,88].

Statement 1.9: Diagnosis of coeliac disease should be based on clinical manifestations, serology and duodenal histology. Positive coeliac-specific antibodies and villous atrophy confirm the diagnosis of coeliac disease.

Strong recommendation, high quality evidence

There is considerable overlap between the gastrointestinal symptoms present in CeD and those of other gastrointestinal diseases. The improvement of symptoms after starting a GFD or their worsening after returning to a gluten-containing diet have a low predictive value for CeD, and should therefore not be used as a criterion for diagnosis, unless supported by other findings. The presence of positive antibodies (IgA anti-tTG and EmA) and villous atrophy confirm the diagnosis of CeD [8,89]. Recent studies have shown that a level of IgA anti-tTG $\geq$ 10 times the upper limit of normality is predictive of villous atrophy. This has opened the way to possible changes in guidelines, as has already occurred in the paediatric setting, to allow CeD to be diagnosed without performing upper GI endoscopy [90,91]. The major doubts come from the possibility that an upper GI endoscopy may diagnose other conditions associated with CeD, such as atrophic or lymphocytic gastritis [92], from the fact that CeD may, even at diagnosis, be associated with complications such as small bowel adenocarcinoma and enteropathy-associated T-cell lymphoma and finally that performing upper GI endoscopy at diagnosis may also be useful should patients not respond to a GFD [93], to allow comparison with follow-up exams. Future studies will probably identify a subgroup of adult patients in whom CeD can be diagnosed without duodenal biopsy, based on well-defined clinical and demographic features. It is essential to underline that patients with severe malabsorption symptoms and a strong clinical suspicion for CeD should undergo upper GI endoscopy with duodenal biopsy regardless of coeliac serology results to exclude/confirm not only seronegative CeD but also other rare forms of villous atrophy unrelated to CeD.

Statement 1.10: Potential coeliac disease should be diagnosed when serology is positive (both IgA anti-tTG and EMA), confirmed at a dedicated laboratory, villous atrophy is absent (reviewed by an expert pathologist) and HLA typing is compatible. The decision to start a gluten-free diet should be taken with the patient and mainly depends on the presence or absence of signs and/or symptoms of disease.

Conditional recommendation, low quality evidence

In the presence of positive IgA anti-tTG with negative histology, testing for IgA anti-tTG should be repeated at a secondary care laboratory, and testing for EmA should also be performed. If on retesting both IgA anti-tTG and EmA are positive, the biopsy should be reviewed by an expert histopathologist. If on histology review the absence of VA is confirmed (*Marsh 0–2, Corazza-Villanacci grade A*), it is then necessary to ensure that the patient was on a gluten-containing diet at time of duodenal biopsy. If it is found that the patient was on a diet with low gluten content, it is recommended to repeat duodenal biopsy 2–6 weeks after a gluten-containing diet is resumed. HLA testing for DQ2 and DQ8 should also be performed.

When positive IgA anti-tTG and EmA with negative duodenal biopsy are confirmed, and HLA testing reveals a genetic predisposition for CeD, this is considered potential CeD (PCD). In confirmed PCD, whether to start a GFD or not should be decided together with the patient, taking into account whether signs or symptoms are present [94–96].

Statement 1.11: An increased IEL count in the absence of villous atrophy on duodenal biopsy (Marsh 1) is not specific for coeliac disease. Marsh 1 with negative serology is not suggestive of CeD.

Strong recommendation, moderate quality evidence

A finding of low-titre IgA anti-tTG, with negative EmA, and Marsh 1 on duodenal biopsy, does not allow for a diagnosis of CeD

Table 4
Differential diagnosis of CeD with and without villous atrophy.

Isolated increase in IEL count without villous atrophy	
Inflammatory bowel disease	Drugs (anti-inflammatory drugs, proton pump inhibitors)
Small intestinal bacterial overgrowth	Autoimmune diseases (rheumatoid arthritis, Hashimoto's thyroiditis, systemic lupus
Blind loop syndrome	erythematosus, multiple sclerosis, autoimmune enteropathy)
Microscopic colitis (lymphocytic and collagenous)	Common Variable Immune Deficiency
Non-coeliac gluten sensitivity	Graft versus Host Disease
Peptic ulcer	Food allergies (cow milk, soy, fish, eggs, etc.)
Duodenitis related to Helicobacter Pylori infection	
Infections (viral gastroenteritis, Giardiasis, Cryptosporidiosis)	
Villous atrophy and increased IEL count	
Infections (tropical sprue, Giardiasis, Whipple disease, Mycobacterium avium, AIDS enteropathy)	Common Variable Immune Deficiency
Collagenous sprue	Graft versus Host Disease
Autoimmune enteropathy	Drugs (mycophenolate mofetil, colchicine, angiotensin II receptor blockers, methotrexate)
Crohn disease	Chemotherapy, Radiotherapy
Eosinophilic gastroenteritis	Immunotherapy (Anti-CTLA4 antibodies)
Small intestinal bacterial overgrowth	Amyloidosis
Enteropathy-associated T-cell lymphoma	

IEL: Intraepithelial lymphocyte.

to be made. Instead, repeating serology after 6–12 months is suggested. Such a strategy may be followed even if clinical suspicion of CeD remains high, assuming that HLA typing reveals a genetic predisposition to CeD.

Lymphocytic duodenitis (Marsh 1) is present in 3.8% of the population with negative serology for CeD [97]. CeD was diagnosed in only 16% of lymphocytic duodenitis cases [98]. Similarly, there are causes of VA on duodenal biopsy other than CeD. Table 4 shows other causes of Marsh 1 and VA. *Helicobacter pylori* infection is frequently associated with Marsh 1 histology. In these cases, the IEL count usually normalises after eradication of *Helicobacter pylori* [99]. Comparison with concomitant gastric biopsies and/or serology is necessary in such cases to clarify the clinical picture.

Statement 1.12: Seronegative coeliac disease should be diagnosed only once other causes of villous atrophy have been excluded. Coeliac specific antibodies, both IgA and IgG, must be negative, HLA typing must be compatible and response to a gluten-free diet after one year must be verified.

Strong recommendation, moderate quality evidence

Seronegative CeD is a rare condition which is often overdiagnosed, with a reported prevalence in the literature ranging from 3% to 15% [100]. The term seronegative CeD should be used for patients with villous atrophy and negative serology for CeD (negative IgA anti-tTG and EmA) with normal levels of IgA immunoglobulins, or, in the presence of IgA deficiency, negative IgG DGP and IgG anti-tTG. HLA typing should reveal a genetic predisposition to CeD, and other causes of villous atrophy must have been excluded [101–103]. In these patients, it is important to evaluate improvement in intestinal lesions after at least one year from starting a GFD, to support the diagnosis of seronegative CeD. Differential diagnosis with other enteropathies, shown in Table 4, requires a comprehensive evaluation of the clinical picture and of histological and genetic findings. It is therefore recommended to refer these patients to a tertiary centre specialised in CeD [104].

Statement 1.13: When patients with suspected coeliac disease are already on a gluten-free diet, gluten challenge is recommended before diagnostic testing for coeliac disease.

Strong recommendation, moderate quality evidence

Normalisation of antibody titres and histological recovery of intestinal lesions are not immediate after initiation of a GFD. However, in patients on a GFD, even for only a few months, negative serology and histology do not rule out CeD, assuming HLA DQ2/DQ8 is present, showing a genetic predisposition to CeD. It is therefore recommended to refer patients already on a GFD to a tertiary centre specialised in CeD for diagnostic testing, where the patient will be able to undergo a "gluten challenge". The patient will be placed on a gluten-containing diet for at least 14 days (preferably at least 6–8 weeks), with at least 3–10 g of gluten per day (equivalent to 2–6 slices of bread), before undergoing duodenal biopsy [105]. A recent randomised controlled trial compared ingestion of 3 g/day of gluten and 10 g/day of gluten, for 14 days, showing that in the majority of cases only 10 g/day induced intestinal lesions [106]. The quantity of gluten ingested and the time required for development of histological intestinal lesions and for coeliac-specific antibodies to become positive may vary from individual to individual. It is therefore useful to perform further serologic testing at a later time point as well.

Other tests

Intestinal permeability tests: although permeability testing (d-xylose testing, lactulose:mannitol ratio) may detect large changes in intestinal permeability associated with CeD, their sensitivity and specificity are subject to significant variability and these tests are not recommended for diagnosing CeD [107].

Imaging and ultrasonography: there are some radiologic and ultrasonographic findings which may be suggestive for CeD, such as a reduction of jejunal folds and an increase in ileal folds, dilation of the small bowel, small bowel wall thickening, intussusception, mesenteric lymphadenopathy (cavitation), vascular abnormalities and splenic atrophy [108–110].

Autoantibody deposits: in a large cohort of coeliac patients and healthy controls it has been shown that the presence of IgA anti-tTG deposits in the small bowel mucosa may be used in selected cases as part of diagnostic testing for CeD [111]. Autoantibody deposits have been found in patients with seronegative CeD as well as in potential CeD. Other possible diagnostic tests include testing for EmA and IgA anti-tTG in cultures of small bowel biopsies [112,113].

Other serological tests: testing for the presence of HLA-DQ-gluten tetramers in blood to detect gluten-reactive T cells [114], and testing for TG2-deamidated gliadin peptide complexes [115].

Fig. 1 shows a flow-chart for the diagnosis of CeD

Section 2. Gluten-free diet

Statement 2.1: Patients diagnosed with coeliac disease should start a strict, lifelong gluten-free diet.

Strong recommendation, high quality evidence

Following a GFD is the mainstay of treatment for CeD. Coeliac patients should not consume foods containing wheat, barley, and rye, or their derivatives [116]. Patients should be instructed on how to correctly read food labels to check whether gluten is

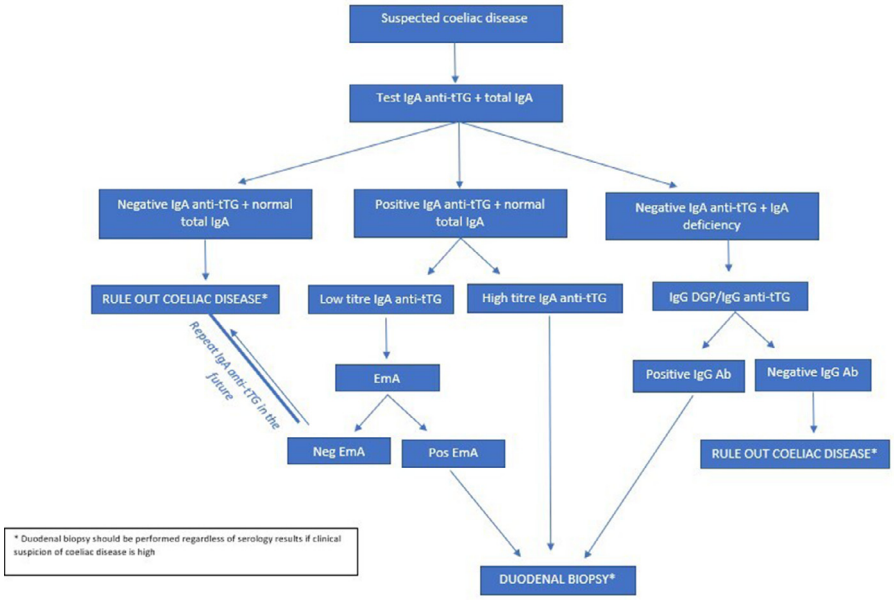

Fig. 1. Flow chart of Coeliac Disease Diagnosis.

present or not in foodstuffs [117]. It is well-known that adherence to a GFD improves in patients who have received better instruction on CeD and on following a GFD. Support from family members and healthcare workers also has a favourable impact [118]. A systematic review of 35 studies suggests that, although the quantity of gluten tolerated varies amongst coeliac patients, a daily dose <10 mg does not seem to induce significant histological lesions [119,120]. The European Commission enshrined in law (EC41/2009), that starting from 2012 gluten-free foodstuffs must contain less than 20 ppm of gluten, an amount considered safe for patients with CeD. amongst cereals, there are several debates on the use of oats. However, oats not contaminated by gluten are safe for the large majority of coeliac patients [121,122]. There is a degree of reluctance in some countries to permit the consumption of oats by coeliac patients, due to difficulties in guaranteeing that oats commercially available are pure and uncontaminated by gluten-containing cereals. In consideration of these risks, it may be advisable to exclude oats from the diet for the first few months after diagnosis.

Adhering to a GFD generally leads to resolution of symptoms [123] and healing of intestinal lesions, as well as a reduction in the risk of developing neoplastic complications [124–126]. Data reported in the literature indicate that strict adherence to a GFD could lead to recovery of an ideal body weight in subjects who at diagnosis were underweight or overweight/obese [127]. Untreated CeD is associated with a high prevalence of low bone mineral density (BMD), which improves once a GFD is started, both in adults and in children [128].

Statement 2.2: Dietary instruction by an expert dietitian, particularly during the initial period when starting a gluten-free diet, is suggested for patients diagnosed with coeliac disease.

Conditional recommendation, very low quality evidence

Once the diagnosis of CeD has been confirmed, patients should be referred to a dietitian for dietary instruction on following a GFD [129,130]. The dietitian should be experienced in the dietary management of CeD and able to correctly instruct patients on how to follow a GFD and should be knowledgeable on alternative gluten-free foods in order to provide patients with a nutritionally-balanced GFD and avoid nutrient deficiencies.

Statement 2.3: Testing for iron andvitamin D is recommended in patients diagnosed with coeliac disease.

Strong recommendation, high quality evidence

Iron-deficiency anaemia is frequent in coeliac patients, occurring in 10–50% of patients at diagnosis [131,132]. A recent meta-analysis found that approximately 1 in 31 patients with iron-deficiency anaemia are affected by CeD [25]. Iron is absorbed by the duodenum and therefore, upon initiation of a GFD and consequent mucosal healing, iron levels gradually normalise in the majority of patients [133]. Carefully following a GFD rich in iron-containing foods, iron stores usually normalise. In a few cases it may be necessary to consider iron supplementation. Folate and vitamin B12 deficiency improve with remission of the underlying enteropathy, although supplementation may necessary should deficiencies persist [134].

Several factors contribute to low levels of vitamin D, including reduced absorption due to fat malabsorption, and removal of milk and derivatives from the diet of coeliac patients with associated lactose intolerance. Studies have shown that vitamin D and calcium levels may normalise after 1–2 years on a rigorous GFD, and that, in some patients, osteoporosis may improve [135]. Calcium and vitamin D should be supplemented in patients with low serum levels, low bone mineral density (BMD), or who cannot guarantee adequate intake from their diet [136]. A recent Italian study found that coeliac patients at time of diagnosis, in comparison to those already on a GFD, have reduced 25(OH)-vitamin D levels, increased parathyroid hormone, and an increased level of $1,25(OH)_2$ vitamin D, which is the active form, but no deficiency in calcium or phosphorus. However, these findings were not associated with abnormal bone metabolism. As a result, no conclusion in favour of an absolute need for vitamin D supplementation at diagnosis was reached [137].

Zinc deficiency may result in growth stunting and reduced protein synthesis (hair loss, and reduced sperm count in men). Once patients start a rigorous GFD, zinc deficiency resolves without a

need for long periods of supplementation [138]. These nutritional deficiencies are more frequently found in adults than in children.

Statement 2.4: Following a nutritionally balanced gluten-free diet is recommended for patients diagnosed with coeliac disease.

Strong recommendation, high quality evidence

Macronutrient and calorie intake in coeliac patients is usually unbalanced, both at diagnosis and during follow-up. The GFD is often lacking in dietary fibre [139] and is, therefore, often associated with constipation. Studies have also found that children on a GFD consumed greater quantities of fats and proteins, as well as more calories, than controls [140]. Many processed gluten-free foods also have a high glycaemic index [141]. Several studies also point out the risk of coeliac patients on a GFD developing metabolic syndrome and fatty liver [142,143]. An increased risk of metabolic-associated fatty liver disease in coeliac patients on a GFD has recently been described [144]. However, other studies have found contrasting results [127,145]. Patients should be informed of these risks and be advised to follow a balanced diet and a healthy active lifestyle.

Section 3. Coeliac disease follow-up

Statement 3.1: A combined evaluation of symptoms, laboratory tests, and serology during follow-up is recommended in all patients with coeliac disease.

Strong recommendation, moderate quality evidence

Statement 3.2: A follow-up duodenal biopsy should be performed in patients with coeliac disease who have persistent symptoms or laboratory test abnormalities while on a gluten free diet.

Strong recommendation, moderate quality evidence

It has been shown that GFD adherence improves over time in patients regularly followed-up at a dedicated centre for CeD [146]. Ideally, both a gastroenterologist and a dietitian with expertise in CeD, should be involved in coeliac patients' care. Patients should be adequately instructed on how to correctly follow-up a strict GFD, and on its importance. Recommending that patients sign up to the national coeliac patients' association may also be helpful for newly diagnosed patients.

In the first year after diagnosis patients should be closely followed-up to optimise GFD adherence and help the patient in adapting to the situation. Once the patient's clinical condition has stabilised and the patient is able to follow the diet without issues, follow-up does not need to be so strict, and may be performed annually or every two years.

At each follow-up medical consultation, the patient's clinical condition and blood test results should be reviewed (full blood count, inflammatory markers, iron status, vitamins, electrolytes, liver and thyroid function, metabolic status) and compared with the clinical picture at diagnosis [33]. Particular attention should be paid to metabolic status, in consideration of the significant risk of developing metabolic syndrome once patients start a GFD [144]. GFD adherence should be evaluated by dietary interview [147] and IgA anti-tTG titres, which should gradually reduce, and eventually become negative [61].

Normalisation of antibody titres is not predictive of histological recovery of villous atrophy, however. A recent meta-analysis found that IgA anti-tTG have a low sensitivity (<50%) in detecting persistence of villous atrophy. As such, better non-invasive markers of intestinal damage for follow-up are needed [148].

Need for follow-up duodenal biopsy should be evaluated on a case-by-case basis. It should be performed in patients with lack of clinical response to a GFD, seronegative CeD, and in those who at diagnosis had factors predictive of an increased risk of developing complications [149]. Age at diagnosis >45 years and a clinical picture of generalised malabsorption are the main predictors of complications [150]. It follows that follow-up modalities for a patient diagnosed at 60 years of age presenting with diarrhoea and weight loss must be different from those for a young adult diagnosed for screening or with only very mild symptoms. In the former case, the patient must be closely followed up at a referral centre for CeD and follow-up duodenal biopsy must be performed.

The first two follow-up medical consultations should be performed at a referral centre (at six and twelve months from diagnosis). No agreement has yet been reached on the ideal setting for continuing follow-up of these patients (referral centre or general practitioner with experience in management of CeD). If complications are suspected, or lack of response to a GFD occurs, patients should be referred to a referral centre as soon as possible.

A possible method to evaluate for dietary gluten contamination may be to test for gliadin immunogenic peptides (GIPs) in urine and/or faeces. In recent years, many studies have shown a high accuracy of these methods in identifying patients with persistent intestinal atrophy [151–153]. A recent Italian study has demonstrated the usefulness of detecting GIPs in urine during the SARS-Cov2 pandemic in symptomatic patients at follow-up [154].

Statement 3.3: Serological screening for coeliac disease is recommended in first-degree family members of coeliac patients. Those with positive serology, or who have symptoms suggestive of coeliac disease, should undergo duodenal biopsy.

Strong recommendation, moderate quality evidence

First-degree and second-degree relatives of coeliac patients should undergo serologic screening for CeD with IgA anti-tTG and measuring total IgA levels to exclude IgA deficiency, regardless of the presence or absence of symptoms [35]. Serologic testing of family members should be performed at time of diagnosis and then every 4 years. Serology should also be performed immediately if symptoms suggestive of CeD occur [155]. Those with positive serology, or with symptoms suggestive of CeD, should undergo duodenal biopsy. In selected cases HLA testing for DQ2/DQ8 can be requested to evaluate whether a genetic predisposition for CeD is present [82].

Statement 3.4: Pneumococcal vaccination is suggested in patients diagnosed with coeliac disease, particularly if comorbidities are present.

Conditional recommendation, moderate quality evidence

Hyposplenism and functional asplenia associated with CeD may result in an ineffective immune response against encapsulated bacteria, leading to an increased risk of certain infectious diseases [156,157]. Hyposplenism is present when spleen size is reduced or when Howell-Jolly bodies are found in peripheral blood [158]. Tienberg et al. have recently reported an increased risk of pneumococcal pneumonia in coeliac patients aged 40–69 years old [157]. Zingone et al. have also recently reported an increased risk of Pneumococcal pneumonia both in adults and in children [156,159]. An increased risk of hospitalisation due to Influenza has also been described [160].

It is therefore reasonable to suggest pneumococcal vaccination in coeliac patients, although conclusive evidence regarding this is lacking. Vaccination for Haemophilus, meningococcus and influenza, should also be suggested. Another aspect to consider is that coeliac patients may have a reduced immune response to vaccination against HBV in comparison to the general population [161,162]. Finally, no increased risk of SARS-CoV-2 infection or of severe disease have been reported in coeliac patients [163–166]. CeD is also not a contraindication for vaccination against COVID-19 [167].

Statement 3.5: Patients diagnosed with coeliac disease who have signs or symptoms of malabsorption, DEXA is recom-

mended at time of diagnosis. All other coeliac patients should be screened for low bone mineral density with DEXA by 30–35 years of age.

Strong recommendation, moderate quality evidence

Statement 3.6: DEXA should be performed every 2–3 years in coeliac patients with low bone mineral density, poor gluten-free diet adherence or persistence of villous atrophy. Coeliac patients with normal bone mineral density should repeat DEXA every 5 years.

Strong recommendation, moderate quality evidence

Coeliac patients have an increased risk of osteoporosis and bone fractures [29,30,168], although not all studies have reported an increased risk of fractures [169,170]. Starting a GFD, in combination with exercise, may lead to an improvement in bone mineral density [171,172]. An improvement in bone mineral density is seen in the first year after starting a GFD [173]. Measuring serum calcium, alkaline phosphatase and vitamin D at diagnosis is recommended, and micronutrient supplementation should be started if deficiencies are detected.

Evaluation of femoral and vertebral bone mineral density using dual-energy x-ray absorptiometry (DEXA) is also recommended. Ideally the first DEXA should be performed at time of CeD diagnosis. This is especially important in patients diagnosed with signs and symptoms of malabsorption, with a significant diagnostic delay, or with a history of bone fractures [174]. In any case, DEXA should be performed in all coeliac patients by 30–35 years of age. It should be repeated every 5 years in patients with normal bone mineral density, and every 2–3 years in those with low bone mineral density, as well as in those with poor GFD adherence or persistent VA. In the most severe cases, IV bisphosphonates may also be used, always in combination with calcium and vitamin D supplementation, to avoid the risk of tetany [174].

Statement 3.7: Evaluating coeliac patients for psychological disorders at diagnosis and during follow-up is suggested and counselling should be provided when required.

Strong recommendation, moderate quality evidence

In recent years significant attention has been placed on the evaluation of quality of life (QOL) in coeliac patients, both at diagnosis and while on a GFD [175]. The majority of studies have found a reduction in QOL at diagnosis, which improves over time once on a GFD. Factors influencing QOL include sex, age, presenting symptoms and GFD adherence. Coeliac patients with gastrointestinal symptoms of malabsorption may be especially impacted by the disease, and this may explain the reduction in QOL described in patients with a classical pattern of disease [176–178]. Persistence of low QOL while on a GFD may be due to dietary restrictions. Nachman et al. have described a reduction in QOL approximately 4 years after diagnosis in those who did not have adequate GFD adherence [179]. An English study has instead suggested that low QOL while on a GFD is related to problems inherent in following a GFD, rather than GFD adherence [180]. A recent meta-analysis found that QOL improves after starting a GFD, that QOL remains lower than controls even after starting a GFD, that at follow-up patients with classical symptoms at diagnosis have a lower QOL and, finally, that patients with good GFD adherence have a better QOL [181].

Associations between CeD and other psychological disorders such as anxiety and depression [182,183], sleep disorders [184], and fatigue [185] have also been reported. Data reported in the literature on the natural history of these disorders in coeliac patients on a GFD are contrasting and it is therefore recommended to monitor patients during follow-up for these disorders [178,184,186–188]. A prospective study has recently reported an improvement of QOL and psychological disorders after one and two years on a GFD, describing dietary compliance as the main risk factor [189,190].

Fig. 2 shows recommendations for the evaluation of coeliac patients at diagnosis and during follow-up.

Section 4. Coeliac disease complications

Statement 4.1: Assuming the initial diagnosis of coeliac disease is certain and other possible causes have been excluded, refractory coeliac disease or other complications should be suspected in patients with persistent or recurrent signs or symptoms of malabsorption despite being on a gluten-free diet for at least one year.

Strong recommendation, moderate quality evidence

Statement 4.2: Patients with suspected refractory coeliac disease should be referred urgently to a specialized tertiary centre. Prednisone/budesonide is recommended as initial treatment.

Strong recommendation, moderate quality evidence

Lack of response to a GFD and the complications of CeD are amongst the most difficult situations to manage from a diagnostic and therapeutic point of view. Data reported in the literature are also very variable, if not contradictory, making the situation even more complex to interpret. Complications have been reported to affect, according to different sources, between 0.2% and 30% of adult CeD patients. Such a wide range in prevalence is due to diverse interpretations of clinical manifestations which may occur in coeliac patients [191]. The authors do not believe that conditions caused by intestinal malabsorption of micronutrients and vitamins (osteoporosis, for example) or associated autoimmune diseases should be included amongst the complications of CeD [192].

Coeliac patients in the vast majority of cases improve markedly both from a clinical and histological point of view after starting a GFD. Clinical improvement should therefore be the first parameter to consider in the follow-up of patients on a GFD. Patients with lack of clinical response, or who present persistent laboratory abnormalities suggestive of ongoing malabsorption, should be referred to a tertiary centre where the initial diagnosis of CeD can be re-evaluated and the possibility of performing a follow-up duodenal biopsy may be considered. If the follow-up duodenal biopsy shows a satisfactory histological response, the occurrence of symptoms while on a GFD may also be due to other aetiologies, such as lactose intolerance, microscopic colitis or irritable bowel syndrome. Their occurrence should not be considered as a lack of response to a GFD, but as a separate entity to be treated independently of CeD [192]. Normal follow-up duodenal biopsy histology (Marsh 0) or minimal lesions (Marsh 1), are supportive of an alternative cause of symptoms. In patients with persistent villous atrophy, it is of paramount importance to ensure that these patients are strictly adherent to the GFD via dietary interview and the use of standardised questionnaires to exclude voluntary or involuntary gluten contamination in the diet. Refractory CeD (RCD) should be considered in patients with persistence or recurrence of signs and symptoms of malabsorption and persistent villous atrophy after following a strict GFD for at least 12 months. These patients should be managed by a tertiary centre. On the basis of an aberrant intraepithelial lymphocyte (IEL) population found on duodenal biopsies with flow cytometry ($CD3^-$ $CD3^{intra+}$ $CD4^-$ $CD8^-$ $CD103^+$) or immunohistochemistry, two forms of RCD can be further defined. Type 1 RCD is diagnosed when this aberrant population is not found in the duodenal biopsy (it is indistinguishable histologically from untreated CeD). On the other hand, the finding of these aberrant IEL allow the diagnosis of type 2 RCD. Clonal T cell receptor gene rearrangements are not specific for Type II RCD, since it can be seen in uncomplicated CeD and Type I RCD. Flow cytometry is considered superior to the clonality analysis and immunohistochemistry in distinguishing the two forms of RCD [193]. Prednisone/Open-

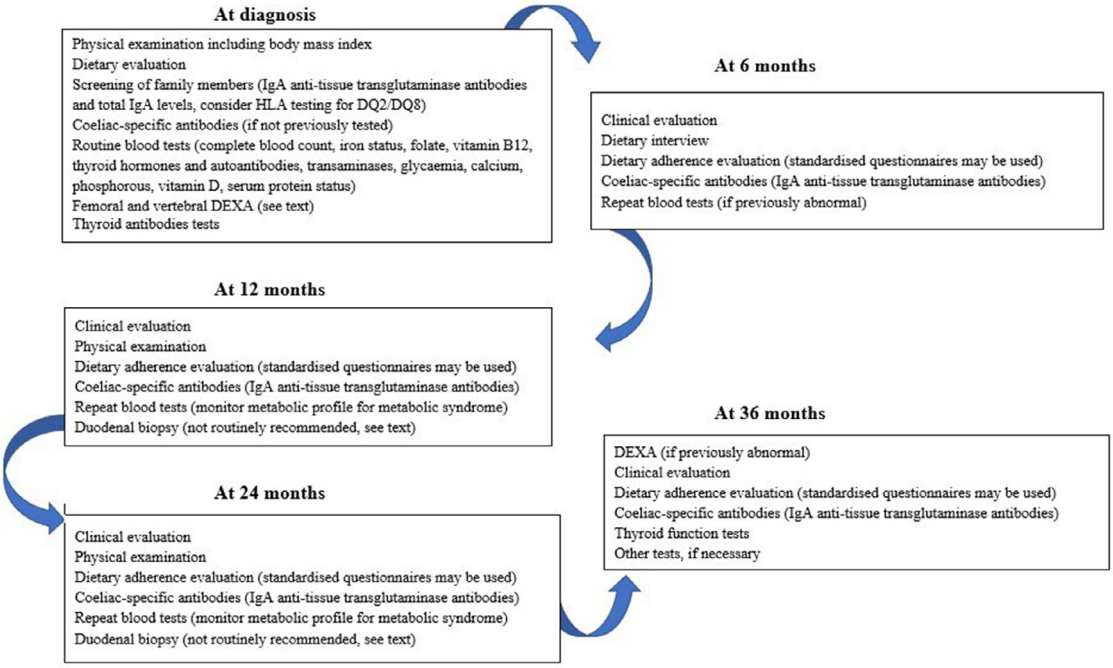

Fig. 2. recommendations for the evaluation of coeliac patients at diagnosis and during follow-up.

capsule budesonide are recommended as initial treatment for both type I and II RCD [193]. Type 2 RCD patients are at risk of progression to ulcerative jejunoileitis or enteropathy-associated T-cell lymphoma (EATL) [193–195]. Last but not least, coeliac patients are also at significantly increased risk of other complications such as small bowel adenocarcinoma, abdominal B cell lymphoma and collagenous sprue [196,198].

Mortality in coeliac patients diagnosed in adulthood is doubled in comparison to the general population. No increase in mortality has been found for coeliac patients diagnosed in childhood or adolescence. The increase in mortality becomes six times greater in patients who do not follow a strict GFD [197]. Poor GFD adherence is the most important predictor of complications. Age at diagnosis and pattern of clinical presentation are also important predictors of complications. Complications of CeD occur almost exclusively in patients diagnosed after 45 years of age and/or for classical symptoms of malabsorption (diarrhoea and/or weight loss) [199].

Complications of CeD should be suspected not only when clinical/histological response to a GFD is lacking, but also in patients who initially responded to a strict GFD with recurrence of symptoms present at diagnosis (diarrhoea, weight loss, anaemia, etc.), despite still maintaining a strict GFD. The onset of unusual symptoms such as fever, gastrointestinal bleeding or significant abdominal pain are other possible indicators of complicated CeD, and should be treated with utmost concern [150,199–201].

Complications of CeD most often occur in the proximal jejunum, although they can occur in any part of the small bowel, or other parts of the abdominal cavity. It is therefore important to carefully study the entire abdomen when complicated CeD is suspected. Capsule endoscopy, enteroscopy and flow cytometry of duodenal/jejunal biopsies to evaluate for an aberrant IEL phenotype are important tests for the small bowel. Other important tests to consider include colonoscopy, abdominal CT/MRI, and positron emission tomography. These patients, due to their significant complexity, should therefore be referred for investigations to a specialised tertiary centre [202,203].

Section 5: Coeliac disease diagnosis and follow-up in children

Statement 5.1: In children with suspected coeliac disease the ESPGHAN criteria should be followed, avoiding duodenal biopsy in those with high IgA anti-tissue transglutaminase antibody titres (>10x upper limit of normality) and positive IgA endomysial antibodies. In all other children (anti-tissue transglutaminase antibody titres<10x or discrepant serology) duodenal biopsy should be performed.

Strong recommendation, high quality evidence

As recommended by the ESPGAN guidelines, testing for IgA anti-tTG, together with total IgA, is the recommended first test when CeD is suspected, both in children with signs/symptoms of CeD and in asymptomatic children in high-risk groups. When total IgA deficiency is present, IgG anti-tTG should be tested, or alternatively IgG DGP antibodies. Diagnosis of CeD can be made without duodenal biopsy in children with IgA anti-tTG titres > 10 times the upper limit of normality, confirmed on a second blood sample with EmA positivity. The family should, in any case, be informed that a confirmatory duodenal biopsy can also be performed if the family or clinician request it. If the aforementioned criteria are not met (IgA anti-tTG titres < 10 times the upper limit of normality, or discrepancy with EmA results), duodenal biopsy is necessary to confirm the diagnosis [20].

If the diagnosis of CeD is not certain, it may be necessary to perform a gluten challenge. It is recommended to avoid gluten challenge during the first 5 years of life and during puberty. Gluten challenge should be preceded by HLA typing and re-evaluation of duodenal histology while on a GFD. The diagnosis of CeD is confirmed if serology becomes positive and there is a worsening of the clinical picture or duodenal histology. If serology remains negative and no histological change occurs after two years on a gluten-

containing diet, CeD should be ruled out, keeping in mind that the disease may still develop in the future [204].

Statement 5.2: Children diagnosed with coeliac disease should start a gluten-free diet only once the diagnosis is certain.

Strong recommendation, high quality evidence

In line with the ESPGAN guidelines, after diagnosis the family should be instructed on how a GFD should be followed by an expert dietitian, if available, or by the physician making the diagnosis. Patients should undergo regular follow-up to monitor clinical improvement and normalization of coeliac-specific antibodies [20]. It is not routinely necessary to perform follow-up duodenal biopsy [205]. If there is an unsatisfactory clinical response to a GFD it is first of all necessary to exclude a lack of adherence to the diet. Further testing should be also be considered in these cases, in some cases including duodenal biopsy. Paediatric coeliac patients should be followed-up at 3–6month intervals for the first year after diagnosis. Follow-up every 12 months is recommended once symptoms have resolved and serology has become negative [206].

Statement 5.3: Adolescents with coeliac disease should gradually transition to adult gastroenterologist care. Transition should be managed with the patient and should include a written report on how the paediatric diagnosis of coeliac disease was made and clinical data on follow-up.

Strong recommendation, moderate level of evidence

The patient and the family should be gradually prepared to transition from paediatric care to adult care. Transition should be a collaborative process involving the patient, parents/carers, physician and dietitian [207–210]. Physical, mental and psychosocial development are fundamental for transition, and vary from individual to individual. The correct timing of transition should therefore also be individualised [211]. One way to facilitate transition of care is to create a "transition report" from the paediatrician [212], which should include details on how the diagnosis was made as well as clinical data during follow-up such as serology, GFD adherence, anthropometric data, and comorbidities. At time of transition to adult care some patients may put in doubt their diagnosis and request a re-evaluation of it, especially if diagnosis is based only on serology, or was made at a very young age. If guideline criteria for diagnosis were not met and the diagnosis must be reconsidered, it may be suggested to retest serology, perform HLA typing, and repeat duodenal biopsy [212].

Section 6. Dermatitis Herpetiformis

Statement 6.1: Direct immunofluorescence on perilesional skin biopsy is recommended in patients with suspected dermatitis herpetiformis. Detection of granular IgA deposits in the dermal papillae confirms the diagnosis.

Strong recommendation, moderate quality evidence

Statement 6.2: Coeliac-specific antibodies and duodenal biopsy are recommended in patients diagnosed with dermatitis herpetiformis to verify the presence of concomitant coeliac disease.

Strong recommendation, moderate quality evidence

Dermatitis herpetiformis (DH) is an autoimmune disease of the skin triggered by gluten ingestion, frequently associated with CeD. Both diseases are triggered by gluten, share the same predisposing HLA haplotypes, and improve with a GFD [2]. The ratio of CeD to DH cases in different populations has been found to be approximately 10–20:1 [213]. The mean age at diagnosis of DH is 39 years (range 11–80 years). Diagnostic work up requires testing for serum IgA anti-tTG and perilesional skin biopsy direct immunofluorescence. The diagnosis of DH is confirmed by a finding on direct immunofluorescence of granular IgA deposits in the dermal papillae. The sensitivity and specificity of such a finding for DH are almost 100%. If the patient is already on a GFD, gluten intake should be resumed and skin biopsy should be repeated at least one month later [214]. If direct immunofluorescence and IgA anti-tTG are both positive, the diagnosis of DH is confirmed. The dermal IgA deposits have been found to target transglutaminase 3 [215]. Patients affected by DH present similar duodenal histologic damage to those found in CeD in 75% of cases, while the remaining cases present only minor abnormalities, as is found in potential CeD. Patients presenting with concomitant CeD and DH have a greater probability of having more severe intestinal lesions than those with a clinical presentation of only DH [216]. Symptoms vary based on whether CeD is present or not. However, the prevalence of nutritional deficiencies, associated autoimmune diseases, and the risk of developing lymphoma are similar in CeD and DH [217].

An Italian study's findings suggest that body mass index may be greater in patients with DH than those with CeD [218], while there is no increased risk of bone fracture in treated DH in comparison to controls [219]. Quality of life appears to be similar in DH patients and controls [220]. Finally, adhering to a GFD reduces all-cause mortality in DH, as in CeD [221].

Statement 6.3: Patients diagnosed with dermatitis herpetiformis should start a strict life-long gluten-free diet.

Strong recommendation, high quality evidence

The cornerstone of treatment in DH is following a strict GFD, resulting in resolution of both cutaneous and gastrointestinal manifestations [222,223]. A long time may be needed for skin lesions to regress completely. Likewise, many years of a rigorous GFD are needed for dermal IgA deposits to disappear. In some patients dapsone may be used for prolonged periods (6–24 months) as an additional treatment until a GFD alone is able to maintain remission of cutaneous lesions. Topical steroids may also be used to control cutaneous symptoms, especially in patients with localised disease, to reduce itching and development of new lesions. If dapsone is unable to control symptoms or significant adverse effects occur, other therapeutic options include sulphasalazine, sulphapyridine and sulphamethoxypyridazine [224,225]. Immunosuppressive drugs including cyclosporin A and azathioprine, colchicine, tetracycline, heparin-nicotinamide, and rituximab, have also been shown to be effective in some reports [225].

Despite strictly adhering to a GFD for a long time, a small percentage of DH patients (approximately 2%) requires continued treatment with dapsone to control symptoms [226]. The term refractory DH has been suggested to describe this condition. No lymphomas or abnormal intra-epithelial lesions have been found in these patients however, making refractory DH a benign condition. Clear histological recovery of intestinal damage occurs in refractory DH, unlike in refractory CeD. Nevertheless, the cutaneous lesions persist, as do dermal deposits of IgA.

Conflict of interest

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Authors' contribution

All the Authors revised and approved the final version of the manuscript.

Supplementary materials

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