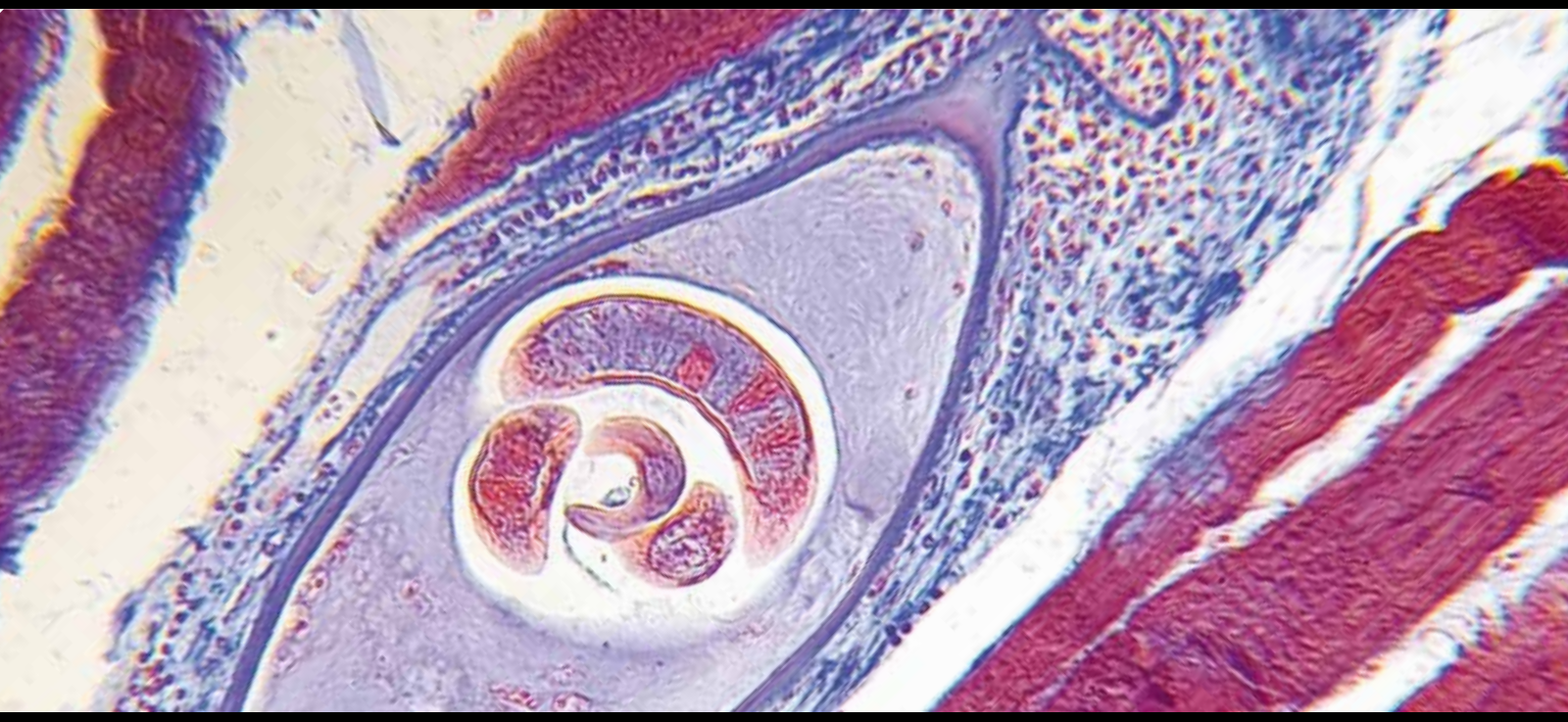
Gastroenterology Research and Practice

Celiac Disease

Guest Editors: Govind K. Makharia, Carlo Catassi, Kheen Lee Goh, and C. J. J. Mulder



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Editorial Board

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Editorial

Celiac Disease

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Celiac disease is a chronic systemic autoimmune disorder induced by gluten proteins present in wheat, barley, and rye. Celiac disease was originally described in 19th century principally in children by Samuel Gee in England and by Christian Herter in the United States. Until the mid-20th century, celiac disease was known as Gee-Herter disease. About two decade ago, celiac disease was considered rare outside Europe and, therefore, was almost completely ignored by health care professionals in rest of the world. The initial diagnostic criteria laid down by the European Society of Pediatric Gastroenterology and Nutrition in 1970 required three sets of intestinal histological evaluation, that is, demonstration of villous atrophy on gluten containing diet, normalization of villous atrophy on gluten-free diet (GFD), and reappearance of villous atrophy on gluten re-challenge. After 1990, relaxation of the diagnostic criteria (reduction in number of biopsies required for the diagnosis from three to one), increase in awareness, and availability of the serological tests; celiac disease in the past 15–20 years has become a global disease and has moved from obscurity into the popular spotlight worldwide.

It was initially thought that gluten hypersensitivity in celiac disease is limited to intestine only and all other features are secondary to malabsorption,but it is now recognized that many of the features of celiac disease may not be explained on the basis of malabsorption alone. It is proposed that the hypersensitivity to gluten is not limited to intestine alone; many other organs are affected independently of intestinal involvement and celiac disease is now considered as a systemic disease. Furthermore, celiac disease is not only one disease caused by gluten; in fact there is a wide spectrum of gluten related diseases. Gluten-related disorders have been classified recently as allergic (wheat allergy), autoimmune (celiac disease, dermatitis herpetiformis, and gluten ataxia), and possibly immune-mediated (gluten sensitivity).

In this special issue on celiac disease, five articles have highlighted various aspects of celiac disease. Approximately 30–50% of patients with celiac disease present to clinicians with features other than gastrointestinal manifestations such as with short stature, hypothyroidism, or type I diabetes to endocrinologists; with refractory anemia to hematologists; or with infertility or delayed menarche to gynecologists. Emami M. H. and coauthors from Iran in this issue have reported celiac disease in 5.9% (9/151) and 1.25% (3/173) of patients presenting with typical and atypical features of malabsorption. B. Admou et al. from Morocco have discussed in a review article about the atypical presentation of celiac disease and how to manage them.

Nine to 72% of patients with celiac disease have low bone mineral density (BMD). On the other hand 4.5–12% of patients having osteoporosis/osteopenia had a positive celiac serology. The low BMD does not always normalize even after years of GFD. This observation suggests that other than malabsorption of calcium and phosphate, other mechanisms are also involved. In an article on bone involvement in celiac disease, T. Larussa et al. from Catanzaro, Italy, have discussed epidemiology, mechanisms, and treatment of bone involvement in patients with celiac disease.

Dermatitis herpetiformis is a cutaneous manifestation of small intestinal immune mediated enteropathy precipitated by exposure to dietary gluten. It is characterised by herpetiform clusters of pruritic urticated papules and

vesicles on the skin, especially on the elbows, buttocks and knees, and IgA deposits in the dermal papillae. While dermatitis herpatiformis is a characteristic gluten-induced skin disease; there are other dermatological manifestations of celiac disease such as vitiligo, alopecia areata, psoriasis, urticaria, atopic dermatitis, and cutaneous vasculitis. C. Marzia et al. from Florence, Italy, have discussed in this issue about the dermatological manifestations of celiac disease.

The management of celiac disease is very different from other gastrointestinal diseases and the core of the treatment is dietary and nonmedicinal. The most effective, most safe and most affordable treatment of celiac disease at present is GFD. While prescribing GFD is easy, both institution and maintenance of compliance to GFD are challenging. The key to success is counseling by a nutrition specialist and maintenance of compliance by the patient. All foods and drugs that contain gluten and its derivatives must be eliminated from the diet because even 50 mg of gluten is sufficient to cause a significant increase in the intestinal mucosal damage.

Patients with celiac disease are more prone to physical, psychological, and social strains than healthy children, which influence the patients health-related quality of life (HRQOL) not only because of disease but also because of restrictions caused by GFD. It can be hard for children, adolescents, or the adult patients with celiac disease to accept and comply with the strict diet. Such an experience to patients with celiac disease affects their quality of life. I. M. Byström et al. from Sweden, in this issue, have described the HRQOL in children and adolescents with celiac disease from the perspectives of children and parents. Children diagnosed before the age of five had higher HRQOL than children diagnosed later. Children who had the classical symptoms of the disease at onset scored better on HRQOL scales than those who had atypical symptoms or were asymptomatic. Moreover, parents of children with celiac disease scored the HRQOL of their children lower compared to that assessed by children themselves.

Celiac disease is one of the ten diseases which are often missed by doctors. Although absolute number of patients with celiac disease at present is not very large, the absolute number is however expected to increase markedly all over the world during the next decade. There are many issues which require immediate attention. The foremost of them include increasing the awareness about the disease amongst doctors and general population. A due emphasis on celiac disease should be placed during undergraduate and postgraduate curriculum. Furthermore, a constant reminder about this disease should be provided to the physicians, internists, gastroenterologists, hematologists, and endocrinologists through continuing medical education.

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Review Article

Atypical Celiac Disease: From Recognizing to Managing

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The nonclassic clinical presentation of celiac disease (CD) becomes increasingly common in physician's daily practice, which requires an awareness of its many clinical faces with atypical, silent, and latent forms. Besides the common genetic background (HLA DQ2/DQ8) of the disease, other non-HLA genes are now notably reported with a probable association to atypical forms. The availability of high-sensitive and specific serologic tests such as antitissue transglutuminase, antiendomysium, and more recent antideamidated, gliadin peptide antibodies permits to efficiently uncover a large portion of the submerged CD iceberg, including individuals having conditions associated with a high risk of developing CD (type 1 diabetes, autoimmune diseases, Down syndrome, family history of CD, etc.), biologic abnormalities (iron deficiency anemia, abnormal transaminase levels, etc.), and extraintestinal symptoms (short stature, neuropsychiatric disorders, alopecia, dental enamel hypoplasia, recurrent aphtous stomatitis, etc.). Despite the therapeutic alternatives currently in developing, the strict adherence to a GFD remains the only effective and safe therapy for CD.

1. Introduction

Celiac disease (CD) is an intestinal chronic inflammatory and autoimmune disease that develops as a result of interplay between genetic, immunologic, and environmental factors [1]. Until recently, CD was considered to be a rare condition, with the highest incidence (1% to 0.3%) in European countries [2, 3]. The true incidence evaluated by a North American study is about 0.5% to 1%, but many, if not most, of studied patients were asymptomatic members of high-risk groups [3, 4]. Recent epidemiological studies performed in North Africa and *Asian* areas also showed a high rate of CD: 0.53% in Egypt [5], 0.79% in Libya [6], 0.6% in Tunisia [7], 0.88% in Iran [8], 0.6% in Turkey [9], and 0.7% in India [10]. The classic form of CD typically presents in infancy and manifests as failure to thrive, diarrhea, abdominal distention, developmental delay, and, occasionally, severe malnutrition [11, 12], which can lead to a true medical emergency [11]. Furthermore, serologic studies demonstrate that most celiac patients present with oligosymptomatic, latent, potential, and extraintestinal forms. These nonclassic clinical presentations become increasingly common and might reach about 50% of all diagnosed patients. The undiagnosed CD cases remain untreated, leaving individuals exposed to the risk of long-term complications, such as infertility, osteoporosis, or cancer [13–16].

Our aim is to emphasize the atypical clinical expression of celiac disease and suggest a diagnosis and managing approach.

2. Genetic Background

As demonstrated by several investigators, CD is one of the most common genetically based diseases; the part of genetic

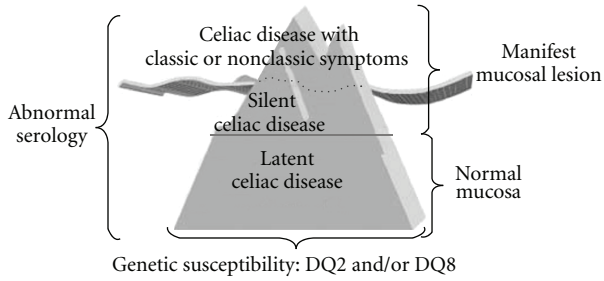


Figure 1: The celiac iceberg model [14].

background is fundamental in its pathogenesis, with possible influence of genetic factors on clinical and immunologic features [17–19]. Approximately 97% of individuals with CD have genetic markers on chromosome 6p21, called class II human leukocyte antigen (HLA). HLA DQ2 predominates, occurring in 90–95% of patients, and HLADQ8 occurs in the remainder [11, 18, 20]. Some studies also point to a correlation between DQ2 homozygousness and female sex, earlier age at diagnosis, shorter time span between onset of symptoms and diagnosis, and to a higher prevalence of classic clinical presentations among patients carrying double-dose DQB1*02 [21]. Other investigations suggest that MHC class I region plays a role in the development of diverse clinical forms of the disease [19, 22]. López-Vázquez et al. [22], thus showed that haplotype B8/DR3/DQ2 is notably overrepresented in atypical CD patients compared to typical ones [19, 22]. In addition, similar studies displayed that MICA-A5.1 allele either is associated with atypical forms of CD in HLA-DQ2-negative patients or confers an additive effect to the DR3/DQ2 haplotype that may modulate the development of the disease [19, 23]. Also, linkage research pointed to chromosomal regions other than the HLA region, predisposing to CD with modest effects; the CTLA4 (cytotoxic T-lymphocyte associated), a closely located gene on chromosome 2q33, is one of these genes [1, 24]. Alongside the HLA, recent genetic studies concerning potential CD patients identified a robust association on chromosome 4q27, involving IL-2, IL-21, and KIAA1109 gene cluster [25, 26], and also c-REL gene [26]. These facts might allow more understanding in CD pathogenesis.

3. Clinical Faces of Celiac Disease

Gee described the classical features of celiac disease in 1887 as diarrhea, lassitude, and failure to thrive [27], but the improvement of knowledge has subsequently disclosed several patterns of the disease [28]. A number of investigators believe that clinically apparent gluten-sensitive enteropathy represents the "tip of the iceberg" of the overall disease burden (Figure 1).

This concept demonstrates the clinical variability of CD and enlightens why the disease remains unidentified in a great proportion of individuals. In fact, the estimated ratio of diagnosed to undiagnosed individuals varies between 1 : 5 to 1 : 8 (the submerged part of the iceberg), usually because of atypical, minimal, or even absent complaints [13, 14].

Many authors defined atypical CD as follows:

(i) *Atypical form*. Absence or few gastrointestinal symptoms, presence of atypical symptoms, such as anemia due to iron deficiency, osteoporosis or osteopenia, infertility, low stature;

(ii) *Silent form*. Occasional diagnosis, histological or serological, in asymptomatic individuals;

(iii) *Latent form, with 2 categories*

(a) patients with previous CD diagnosis who responded to gluten-free diet (GFD) and presented a normal histology or only intraepithelial lymphocytes increase,

(b) individuals with normal intestinal mucosa, under diet including gluten, who will subsequently develop CD;

(iv) *Refractory form*. Patients with CD who do not respond to GFD [12, 14, 29].

Patients with CD are diagnosed at any age and can exhibit a wide range of clinical manifestations (Table 1). In fact, beyond infancy, the symptoms of CD tend to be less dramatic [30, 31]. Older children may present with constitutional short stature or dental enamel defects, and women comprise approximately 75% of newly diagnosed adult CD cases, with more clinically conspicuous disease [11, 31].

Evidence suggests that the incidence of CD increases with age even in older patients [33]. Indeed, the majority of the elder cases remains undetected, often due to the absence of symptoms or because of atypical clinical presentations [34, 35]. Osteoporosis represents one of the most frequent revealing circumstances of the disease in the elderly, and the rate of bone loss is accelerated in women after the menopause, likewise in men at the same age [33, 36]. Anyway, physicians' lack of alertness in the older people may result in a significant delay in diagnosis, as CD is widely deemed to be a condition affecting younger subjects [33].

Moreover, a wider spectrum of neurologic syndromes may be the presenting extraintestinal manifestation of gluten sensitivity with or without intestinal pathology. These include headache, ataxia and psychiatric disorders [29], migraine, encephalopathy, chorea, brain stem dysfunction, myelopathy, mononeuritis multiplex, Guillain-Barré-like syndrome, and neuropathy with positive antiganglioside antibodies [37]. Additional studies showed high prevalence of gluten sensitivity in genetic neurodegenerative disorders such as hereditary spinocerebellar ataxia and Huntington's disease [37]. As well, oral manifestations, mostly recurrent apthous ulcers or stomatitis and dental enamel hypoplasia or defects, are atypical signs of CD, and should be considered, even in the absence of any gastrointestinal symptom, at-risk subjects, and should therefore undergo diagnostic procedure for CD [28, 38]. Also, recurrent febrile infections associated to moderate neutropenia must be included in the diagnostic workup for atypical/silent CD in the general population [39]. Furthermore, many of biologic abnormalities either concur with CD or at times may reveal the disease such as

Table 1: Clinical and biological revealing circumstances of atypical CD.

Atypical clinical symptoms
Anemia
Unclear vomiting
Constipation
Recurrent abdominal pain
Short stature
Irritability and impaired school performance
Impaired physical fitness and chronic fatigue
Osteopenia/osteoporosis/arthtritis
Dermatitis herpetiformis
Dental enamel hypoplasia
Recurrent aphtous stomatitis
Headache
Peripheral neuropathy
White matter lesions
Cerebellar ataxia
Epilepsy
Intracranial calcifications
Autism
Psychiatric disorders
Depression
Pubertal delay
Recurrent abortions
Infertility
Biologic abnormalities
Anemia, iron deficiency; vitamin B12 and/or folate deficiency
Hypertransaminasemia
Hyperalkaline phosphatase level
Hyperalbuminemia
Hypercalcaemia, hypophosphatemia
Thrombocytosis, leukocytosis
Coagulopathy
Low high-density and low-density lipoprotein cholesterol levels

Table 2: List of possible celiac-disease-linked pathologies.

Associated autoimmune diseases or other conditions
Type 1 diabetes
Thyroid disorders (autoimmune or graves)
Liver disease (autoimmune hepatitis, primary biliary cirrhosis)
Myasthenia gravis
Primary biliary cirrhosis
Primary sclerosing cholangitis
Psoriasis
Sjögren disease
Systemic lupus erythematosus
Idiopathic dilated cardiomyopathy
Immunoglobulin A nephropathy
Lymphocytic or microscopic colitis
Autoimmune Addison's disease
Rheumatoid arthritis
Vitiligo or alopecia areata
Associated genetic diseases
Down syndrome
Turner syndrome
Williams syndrome
IgA deficiency
Commun variable immunodeficiency

anemia with iron, vitamin B12 and/or folate deficiencies, hypertransaminasemia (Table 1).

The prevalence of CD has increased sharply in recent years because of better recognition of the disease and its associated disorders (Table 2) [18, 36, 40]. A number of diseases seem to occur more commonly in CD. Many studies showed that patients with type 1 diabetes mellitus (T1DM), autoimmune thyroid disease, Sjögren's syndrome, primary biliary cirrhosis, Addison's disease, systemic lupus erythematosus, and alopecia areata may also exhibit similar genotypes of the celiac disease (HLA-DQ2 [DQA1*0501 and DQB1*0201]) and are at risk for gluten-sensitive enteropathy [11]. Autoimmune disorders occur 3 to 10 times more frequently in those with celiac disease than in the general population. Evidence exists that the risk of developing other autoimmune conditions increases with length of exposure to gluten [11, 18, 41]. Among associated CD conditions, T1DM is probably the most important; occurring in about 5% of CD patients [40, 42], with a large variance between ethnic populations (range: 0.97–16.4%) [43]. In addition, unexplained and recurrent hypoglycemia in well managed diabetic individuals should alert the physician for CD screening [44]. Approximately 5% of the patients with CD have thyroid disorders (either autoimmune (Hashimoto's) or Graves's disease) [42], and the ISPAD (International Society for Pediatric and Adolescent Diabetes) clinical practice consensus guidelines 2006-2007 recommend an assessment of the thyroid function at the diagnosis of CD and thereafter every second year in asymptomatic individuals and also a screening for CD at time of the diagnosis of these thyroid disorders and every second year thereafter [45, 46]. Down or Turner syndromes also represent frequent linked conditions in which CD is often asymptomatic and then require systematic screening for CD [47, 48]. Furthermore, the association of some primary immunodeficiencies entities with CD has been described such as IgA deficiency [49] and common variable immunodeficiency [50].

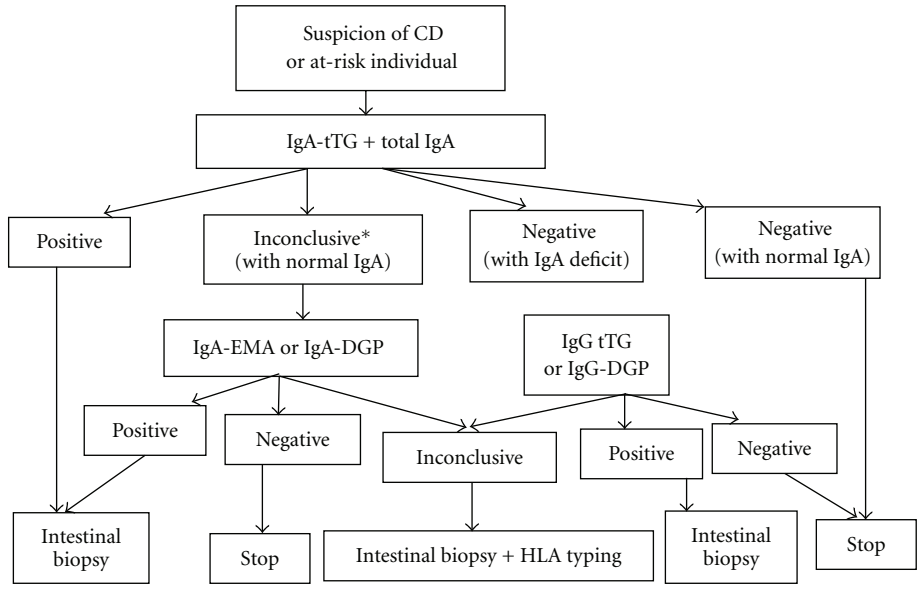
4. Serologic Testing: Performances and Limits

Since the introduction of serological tests, and because of occasional screening, silent CD forms have been increasingly recognized. This is frequently the case of family predisposed individuals, and patients with associated autoimmune or genetic disorders. In CD, highly sensitive and specific methods are nowadays widely used in laboratory testing such as antiendomysial (EMA) and antitissue transglutaminase (tTG) antibodies tests [18, 51]. But, although these tests exhibit very high sensitivity and specificity [11, 13, 32],

Table 3: Characteristics of exclusive or combined serological tests used to detect CD [11, 13, 18, 32].

Serological tests	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
IgG AGA	57–78	71–87	20–90	40–90
IgA AGA	55–100	65–100	30–100	70–100
IgA EMA	86–100	98–100	98–100	80–95
IgA tTG	90–96	91–97	>90	>95
IgA tTG and EMA	98–100	98–100	>90	>95
IgA DGP	98	94	92	98
IgG DGP	97	100	100	97
IgA DGP + IgA tTG	100	93	91	100
IgG DGP + IgA tTG	100	97	97	100

IgG: immunoglobulin G; IgA: immunoglobulin A; AGA: antigliadin antibodies; EMA: endomysial antibodies; tTG: tissue transglutaminase; DGP: deamidated gliadin peptide; PPV: positive predictive value; NPV: negative predictive value.



*Contrast between clinical data and serologic markers results

Figure 2: Algorithm proposal for biologic diagnosis of celiac disease.

recent investigations showed that their accuracy remains controversial in some conditions; sensitivity is considered unacceptable both in patients with minor degrees of mucosal damage and in cases with silent or oligosymptomatic forms [32]. Moreover, EMA and tTG have been found to be superior to AGA (anti-gliadin antibodies) tests [11, 13, 18] and when used in combination have sensitivity and specificity greater than 95% [11, 13]. In addition, the recently developed deamidated gliadin peptide (DGP) antibody test shows promise in CD diagnostic [32, 51], and its performances are comparable to those of IgA-anti-tTG [52, 53]. Moreover, IgG anti-DPG test has high diagnostic sensitivity not only in IgA-competent but also in IgA deficient CD patients [52]. Therefore, a combined evaluation of IgA-anti-tTG, and IgG anti-DPG seems to be adequate for serodiagnosis of CD irrespective of IgA deficiency and without the need for estimating total IgA concentrations [52, 53]. The detection characteristics for AGA, EMA, tTG, and DGP tests are shown in Table 3. In practice, according to new recommendations, the initial serology testing consists on IgA-tTG screening, combined to total serum IgA measurement in order to rule out individuals with potential IgA deficiency. The serology test should be performed before eliminating gluten from patient's diet [54]. Actually, the biologic diagnosis should be improved by combining two performant serologic markers, such as IgA-tTG and -EMA or IgA-tTG and IgG-DGP according to suggested algorithm in Figure 2. The patients who test positive with these assays are consequently candidates for diagnostic endoscopy and small-bowel biopsy [51]. However, besides the atypical clinical expression of CD, the diagnosis may be more difficult for many reasons: negative serology, irregular histological behavior, or inadequate number or place of biopsies [55].

Despite the evolving performances of these serologic testing, there are still significant problems concerning the diagnosis approach in some atypical conditions; for example,

it has been proposed that IgG-AGA testing might be the best marker for neurological manifestations of gluten sensitivity, mainly for patients with sporadic ataxia [60, 61]. Thus, in a recent study on gluten ataxia patients, Hadjivassiliou et al. [62], noticed anti-EMA antibodies in only 22% of patients, and anti-TG2 IgA in up to 38% of cases, but often at lower titres than those seen in patients with gluten sensitivity enteropathy [62]. On the other hand, the serology is generally thought to be unreliable in children <18 months of age [63]. This is due to a number of factors including the high proportion of children on breast milk, lower IgA levels, and the under-developed immune system. Some authors have suggested that IgA-AGA may be useful in this situation. This view is supported by a recent study carried out in 208 children <18 months of age diagnosed with CD [64], showing a better sensitivity of IgA-AGA compared to both the IgA-tTG and IgA EMA [65, 66].

5. Seronegative Celiac Disease

Not all patients have positive CD serologic markers at presentation [67, 68]. In fact, the presence of related CD antibodies correlates with the degree of villous atrophy and possibly the mode of presentation of the disease [67, 69]. Patients with lesser degrees of villous atrophy are less likely to have positive celiac serology [18], and patients who present persistently positive serology and negative biopsy probably have latent CD [12]. Moreover, children younger than 2 years of age lack EMA and tTG antibodies; for this reason, serological testing in children younger than 5 years of age may be less reliable and requires additional investigation [18]. On the other hand, in individuals who are IgA-deficient, the measurement of IgG-EMA and anti-tTG offers reliable results with excellent sensitivity (close to 100%) and specificity [12, 18]. Anyway, if CD suspicion is high with persistently negative tests, individuals must perform typing for HLA and, if positive, they must perform duodenal biopsy or alternatively perform biopsy directly [12, 55].

6. Histopathologic Findings

The intestinal biopsy represents the gold standard diagnosis for CD [12, 55]. According to Marsh-Oberhuber's [56, 57] criteria (Table 4), the spectrum of alterations compatible with CD consists of intraepithelial lymphocytic (IEL) infiltration, pattern of crypts, and villous atrophy, and patient's symptoms frequently correlate with the degree of tissue injury [59]. However, IEL increase with normal mucosa architecture may be observed in autoimmune diseases, such as SLE, rheumatoid arthritis, and Hashimoto's thyroiditis, in patients using nonhormonal anti-inflammatory treatment, in CD's initial presentation, and latent CD [55, 70]. An increase in IEL may also reflect a state of T cells activation triggered by gluten, immune abnormalities, drugs, and infectious agents. Celiac patients, who present only IEL increase with no alterations in the architecture of the mucosa, may be symptomatic and be under increased complications risk [12]. Similarly, villous atrophy may be due to other causes such as Crohn's disease, collagenous sprue, and autoimmune enteropathy [71]. Moreover, a recent prospective evaluation led by different expert pathologists highlighted that a recently proposed three-grade classification system [58] gives better interobserver agreement as compared with the established six-grade Marsh-Oberhuber classification (Table 4) [72].

Table 4: Histopathologic classification of CD based on Marsh-Oberhuber [56, 57], and Corazza and Villanacci [58] new grading system [12, 57, 59].

Marsh-Oberhuber classification
(i) Marsh I: infiltrative lesion, normal villous architecture and mucosa, and IEL increase (>30–40 lymphocytes/enterocytes counted).
(ii) Marsh II: hyperplasic lesion; similar to Marsh I with crypt hyperplasia.
(iii) Marsh III: destructive lesion, subdivided to the following:
(a) partial villous atrophy,
(b) subtotal villous atrophy,
(c) total villous atrophy.
New grading system
(i) Grade A (nonatrophic): >25 IELs/100 enterocytes.
(ii) Grade B (atrophic): villous-crypt ratio <3 : 1.
(iii) Grade B2 (atrophic): no detectable villi.

Similarly to wide variation in clinical manifestations, GSE has a wide spectrum of histological abnormalities, which makes interpretation of small-intestinal biopsy specimens problematic for the pathologist [73]. Therefore, it is not advised to affirm a diagnosis based only on the histological findings, because the disease does not compromise uniformly intestine, and alterations are not observed exclusively in CD [12, 55]. Actually, many differential diagnoses (Table 5) may give rise to CD, making the diagnosis more difficult.

7. HLA Typing

All CD patients carry HLA-DQ2 or HLA-DQ8 [20]. However, up to 40% of the general population also carries these HLA haplotypes. Their presence is necessary for the development of celiac disease, but the absence of these alleles virtually excludes the diagnosis [18] with a negative predictive value for CD close to 100% [20]. HLA typing represents the first step for investigating relatives of CD patients, specifically 1st-degree relatives and then permits to identify individuals for evaluation with biopsy [12]. In practice, if CD suspicion is high, with persistently negative tests, individuals must perform typing for HLA and, if positive, they must perform duodenal biopsy or alternatively perform biopsy directly. Likewise, HLA typing is indicated in individuals who refuse to undergo biopsy [12].

8. Gluten-Free Diet: Indications and Managing

An increased incidence of small-bowel malignancies, adenocarcinoma, and enteropathy-associated T-cell lymphoma has been reported in untreated CD [18, 74].

Table 5: Celiac disease differential diagnosis [12].

Anorexia nervosa
Autoimmune enteropathy
Bacterial overgrowth
Collagenous sprue
Crohn's disease
Giardiasis
HIV enteropathy
Hipogammaglobulinemia
Gastroenterite infecciosa
Intestinal lymphoma
Radiation enteritis
Ischemic enteritis
Lactose intolerance
Common variable immunodeficiency
Soy protein intolerance
Tropical sprue
Tuberculosis
Whipple's disease
Zolliger-Ellison syndrome
Eosinophilic gastroenteritis

Table 6: Indications of GFD in CD of children and adolescents [75].

CD clinical form	Indications of GFD
Symptomatic	Therapeutic
Silent	Preventive: may be discussed
Latent	Surveillance

A strict and lifelong gluten-free diet (GFD) has been demonstrated to be effective and safe, preventing most potential complications of the disease, including autoimmune disease, osteoporosis, infertility, prematurity, and malignancy [76, 77]. However, there is still no evidence that patients who have symptom-free celiac disease are at increased risk of small-intestinal lymphoma or other complications [71]. On the other hand, diet trials in patients with gluten sensitivity and neurologic syndromes have shown variable results and have been inconclusive in some neurologic diseases such as autism and schizophrenia [37]. Furthermore, in asymptomatic patients, a second follow-up biopsy under a GFD is advised to demonstrate the histological recovery of the mucosa, which usually does not develop before six months [73].

In general, the guidance of GFD may be envisaged according to three modalities (Table 6).

(i) Typical or symptomatic CD; GFD is a formal therapeutic indication.

(ii) Silent CD; GFD is discussed under two circumstances.

(iii) Silent CD discovered on the occasion of a serological screening in the family of a celiac or in a patient at risk (diabetes mellitus, dermatitis herpetiforme); in this case, the lesser clinical or nutritional sign would treat the subject as symptomatic and plead in favor of GFD.

(iv) CD becoming silent in the second childhood after that the active disease in the first childhood was treated several years by a well monitoring GFD.

In these two situations and in individual really clinically and biologically asymptomatic, the decision to introduce or to resume the GFD is then rather preventive.

(v) Latent CD (subjects genetically predisposed with normal intestinal mucosa); a simple clinical and biological surveillance is advocated by recent studies [75].

Beside the GFD, the management of many of CD-linked features may require additional supplementation particularly in nutritional problems, such as lower Hb and low Fe, low albumin or Ca, cholesterol and folates disorders [32, 78–80]. Likewise, in CD patients with low bone mineral density, apart from a GFD, a rational managing should follow conventional lines, including increasing exercise, stopping smoking, and avoiding alcohol excess and ensuring an adequate Ca intake using supplements if necessary [36]. In addition, newly therapeutic alternatives are currently interested in the pathogenesis of the disease, focusing on engineering gluten-free grains, degradation of immunodominant gliadin peptides that resist intestinal proteases by exogenous endopeptidases, decrease in intestinal permeability by blockage of the epithelial zonuline receptor, inhibition of intestinal tTG2 activity by transglutaminase inhibitors, inhibition of gluten peptide presentation by HLA-DQ2 antagonists, modulation or inhibition of proinflammatory cytokines, and induction of oral tolerance to gluten [14, 81, 82]. But, at this time, strict adherence to a GFD remains the only effective and safe therapy for CD [14].

9. Refractory Celiac Disease

A small proportion of CD patients fails to improve after a GFD and may be considered as atypical regarding their outcome [14, 83]. Refractory celiac disease (RCD) was recently defined as persisting or recurring villous atrophy with crypt hyperplasia and increased intraepithelial lymphocytes (IELs) in spite of a strict GFD for more than 12 months [71, 84]. It can be either primary, as lack of initial response to diet, or secondary, as unresponsiveness to diet in the form of a relapse [73]. Two categories of RCD are recently being recognized: type I without aberrant T cells and type II with aberrant T cells [85]. The presence of an aberrant clonal intraepithelial T-cell population and/or loss of antigen on IELs seem to characterize population on high risk for development of overt lymphoma and differentiates RCD II from RCD I, which shows low or almost absent aberrant T cells [84].

To manage RCD, Krauss and Schuppan [71] recommend firstly to reassess the diagnosis of CD in order to exclude other diseases, such as giardiasis, tropical sprue, post-infectious diarrhea, collagenous sprue, protein intolerance or protein-losing enteropathy, tuberculosis (including atypical), AIDS, common variable immunodeficiency syndrome,

Whipple's disease, ulcerative jejunitis, lymphocytic colitis, radiation enteritis, immunoproliferative small-intestinal disease, Crohn's disease, eosinophilic gastroenteritis, and autoimmune enteropathy [71, 84], and then to check for errors in diet or compliance [71]. The treatment of RCD I consists of a first-line immunosuppressive therapy based on azathioprine after induction of clinical remission with corticosteroids [86]. A second-line therapy (Cyclosporine A, infliximab, tacrolimus) is suggested in case of clinical deterioration despite corticosteroid therapy or intolerance to azathioprine [87] RCD II is usually resistant to medical therapies, and facing persistent clinical symptoms and/or a high percentage of aberrant T cells in intestinal biopsies in spite of a corticosteroid treatment, more aggressive therapeutic schemes should be considered [84].

10. Conclusion

Celiac disease represents a prototype of disease from which science and medicine take advantage, offering more and uninterrupted understandings both in genetic, clinic, diagnosis, and management aspects. Against its potential complications, the real challenge is to recognize asymptomatic or oligosymptomatic CD cases. The diagnosis should also be improved by a process of case finding focused on at-risk groups.

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Review Article

Bone Mineralization in Celiac Disease

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Evidence indicates a well-established relationship between low bone mineral density (BMD) and celiac disease (CD), but data on the pathogenesis of bone derangement in this setting are still inconclusive. In patients with symptomatic CD, low BMD appears to be directly related to the intestinal malabsorption. Adherence to a strict gluten-free diet (GFD) will reverse the histological changes in the intestine and also the biochemical evidence of calcium malabsorption, resulting in rapid increase of BMD. Nevertheless, GFD improves BMD but does not normalize it in all patients, even after the recovery of intestinal mucosa. Other mechanisms of bone injury than calcium and vitamin D malabsorption are thought to be involved, such as proinflammatory cytokines, parathyroid function abnormalities, and misbalanced bone remodeling factors, most of all represented by the receptor activator of nuclear factor B/receptor activator of nuclear factor B-ligand/osteoprotegerin system. By means of dual-energy X-ray absorptiometry (DXA), it is now rapid and easy to obtain semiquantitative values of BMD. However, the question is still open about who and when submit to DXA evaluation in CD, in order to estimate risk of fractures. Furthermore, additional information on the role of nutritional supplements and alternative therapies is needed.

1. Epidemiology of Bone Involvement in CD

Since 1980s, the most widely used tool in osteoporosis detection, treatment, and follow-up has been dual-energy X-ray absorptiometry (DXA) which showed a strong correlation between detection of bone mineral density (BMD) and fracture risk. Other procedures used to assess BMD include dual-photon absorptiometry (DPA), quantitative computed tomography (QTC), and ultrasound [1]. World Health Organization criteria for osteopenia and osteoporosis are defined by means of BMD as currently assessed by DXA indicating, respectively, a T score between -1 and -2.5 and ≤ 2.5. Both these conditions consist of a quantitative and qualitative alteration in the arrangement of bone tissue with a consequent increase in bone fragility and susceptibility to fracture [2].

Several studies evaluated bone status in celiac disease (CD), both at diagnosis and after gluten-free diet (GFD), and to date, it has been recognized that bone involvement may be a frequent finding during CD. Nevertheless, studies focusing on the prevalence of bone derangement in celiac patients are still inconclusive since both old and recent findings fall in a wide range ([3–11], see Table 1).

On the other hand, the prevalence of CD in idiopathic osteoporotic patients has been investigated in many studies, but controversy still does exist about the value of screening for CD in this setting. Duerksen and Leslie [12] observed that adult women who were positive for antibody testing for CD had lower BMD than the seronegative control group. Stenson et al. [13] reviewed screening results for CD in osteoporotic patients and found a 3.4% incidence of CD compared to 0.2% among general population in subjects without gastrointestinal symptoms. In 1992, Lindh et al. [14] screened 92 patients with osteoporosis for CD showing that 11 (12%) had elevated levels of serum IgA antibodies to gliadin, while only three of them displayed CD-related intestinal lesions. More recently, among 135 patients with low BMD evaluated by Karakan et al. [15], 13 (9.6%) displayed positivity for IgA antiendomysial antibodies, but

Table 1: Prevalence of low bone mineral density in patients with celiac disease as assessed by dual-energy X-ray absorptiometry scan at spine.

Authors	Patients characteristics	Low BMD
*McFarlane et al., 1995 [3]	No. 65, on GFD	47%
Walters et al., 1995 [4]	No. 34, on GFD	38%
Valdimarsson et al., 1996 [5]	No. 63, untreated	38%
Bai et al., 1997 [6]	No. 25, untreated	72%
*Kemppainen et al., 1999 [7]	No. 77, on GFD and untreated	26%
Sategna-Guidetti et al., 2000 [8]	No. 86, untreated	66%
Meyer et al., 2001 [9]	No. 128, on GFD and untreated	72%
Motta et al., 2009 [10]	No. 31, on GFD	9%
Vilppula et al., 2011 [11]	No. 35, untreated	62%

BMD: bone mineral density; GFD: gluten-free diet.
*Established as osteoporosis.

Table 2: Prevalence of positive serology for celiac disease in patients with low bone mineral density.

Authors	Positive serology for celiac disease
Lindh et al., 1992 [14]	11 out of 92 (12%)
Mather et al., 2001 [16]	7 out of 96 (7.3%)
Stenson et al., 2005 [13]	12 out of 266 (4.5%)
Karakan et al., 2007 [15]	13 out of 135 (9.6%)

histological examination of intestinal mucosa was normal in all of these patients. Also, Mather et al. [16] did not detect an increased prevalence of CD among 100 consecutive patients referred for evaluation of low BMD. Indeed, despite a high rate of weakly positive IgA antiendomysial antibodies tests (7.3%), none of these subjects showed histopathological features of CD at the small bowel biopsy. Data are summarized in Table 2. Therefore, a screening strategy for CD in subjects with reduced BMD does not seem to have a major role in order to identify a secondary cause of bone impairment. Furthermore, clinicians should take into account the cost of CD serology tests that precludes their large-scale use. Maybe, screening tests for CD in idiopathic osteoporosis should be addressed to selected patients with no evidence of well-established risk factors for osteoporosis (i.e., younger, premenopausal, male gender patients).

2. Pathophysiology of Bone Metabolism in CD

2.1. Bone Metabolism in Adults. Individual's gender, constitution, and age as well as variations in endocrine systems associated with factors such as menopause and presence of comorbidities can all interact with lifestyle factors, including smoking, lack of exercise, and low dietary calcium intake to determine the onset of osteoporosis [17].

Bone is a dynamic tissue continuously renewed in a process called bone remodeling which is highly regulated by means of a complicated mechanism. However, the peculiar molecular pathways that control its initiation, progression, and cessation remain poorly understood. A leading role relies on two types of cells: osteoclasts, which are differentiated monocyte-derived cells involved in the removal of bone matrix, and osteoblasts, which derive from mesenchymal stem cells and are capable to form new bone. In the third decade of life, the process of bone resorption begins to exceed bone formation, and this fact leads to a progressive bone loss [18].

Nutrition plays an important role in bone homeostasis, providing the necessary substrates for the metabolic functions of bone tissue, most at all vitamin D and minerals. Vitamin D regulates intestinal calcium absorption by stimulating the formation of specific proteins that transport calcium through enterocytes, called calbindin and calcium-binding proteins. There are two forms of vitamin D: D3 (cholecalciferol) and D2 (ergocalciferol). Both forms are biologically activated in humans by hydroxylation first in the liver, to form 25-hydroxyvitamin D (25-[OH]D), and then in the kidneys, to form 1,25-dihydroxyvitamin D (1,25-$[OH]_2$D). Even with low biological activity, 25-(OH)D is the main circulating form of vitamin D; therefore, blood 25-(OH)D concentrations are generally thought to reflect nutritional status regarding vitamin D. Furthermore, reduced calcium intake or malabsorption leads to increased parathyroid hormone (PTH) secretion which promotes bone turnover and cortical bone loss. PTH and 1,25-$(OH)_2$D are linked in a series of coordinated activities to maintain normal serum calcium levels. When circulating calcium is reduced, the parathyroid glands increase the secretion of PTH, which in turn increases the circulating levels of 1,25-$(OH)_2$D, by stimulating the renal hydroxylation of 25-(OH)D. This is the reason why increased 1,25-$(OH)_2$D levels may be observed in CD [19].

2.1.1. Malabsorption. The impact of nutrient malabsorption caused from untreated CD is well documented. In patients with symptomatic CD, the main cause of low BMD is related to the state of malabsorption. Impaired absorption of calcium during CD is thought to result principally from loss of villous in the proximal intestine, where calcium is most actively absorbed. Adherence to a strict GFD will reverse the histological damage in the intestinal mucosa and also the biochemical evidence of calcium malabsorption, as

demonstrated with the use of strontium test by Molteni et al. [20]. However, vitamin D receptors are normally expressed in the duodenal mucosa of celiac patients, even in the presence of villous atrophy, suggesting that additional mechanisms other than calcium malabsorption due to villous atrophy are possibly involved in bone injury [21]. Pazianas et al. [22] showed a reduced fractional calcium absorption compared with controls in female patients on GFD from a mean duration of 4.7 years, notwithstanding variable degrees of improvement of intestinal mucosa. In this regard, it is not secondary to consider the role of the unabsorbed fatty acids in celiac patients. Indeed, intraluminal fats bind calcium in the intestinal lumen and may reduce dietary vitamin D absorption. Staun and Jarnum [23] showed a lack of calbindin and calcium-binding protein, the vitamin D-regulated proteins implicated in calcium uptake from the intestinal lumen, in the areas of damaged mucosa.

2.1.2. PTH and Hormone Disorders. It is well recognized that an excess of PTH can be associated with bone loss. Selby et al. [24] demonstrated a reduced BMD related to secondary hyperparathyroidism without vitamin D deficiency in patients on GFD. In a prospective study by Valdimarsson et al. [25], patients with initial secondary hyperparathyroidism displayed low BMD up to 3 years after GFD suggesting that different pathways in bone homeostasis of celiac patients are involved other than calcium malabsorption due to gluten-related damage of intestinal mucosa.

On the other hand, Lemieux et al. [26] performed a study on 17 treated celiac patients in order to assess the relationship between PTH levels, parathyroid function abnormalities, and bone loss. They confirmed a reduced BMD in all patients notwithstanding a 5.7-year mean period of GFD, but PTH values, although higher than in control group, were still in the normal range. Results regarding parathyroid functional studies were similar in both celiac and control group, excluding a residual secondary hyperparathyroidism in treated celiac patients.

Celiac males are also at greater risk of infertility and hypogonadism. In this case, CD patients are more likely to develop osteoporosis. On the other hand, hypogonadism in men may be often associated with hyperprolactinemia; thus, the occurrence of bone loss can be due to secondary increased levels of estrogens. Controversial opinions do exist about testosterone therapy in men for the prevention and treatment of osteoporosis. Nevertheless, it has been shown that men with osteoporosis and concomitant hypogonadism, as well as those with CD associated, may obtain beneficial effects from this treatment [17].

2.1.3. Proinflammatory Cytokines. Recent studies showed that chronic release of proinflammatory cytokines, hormonal components, and other misbalanced bone remodeling factors can predispose celiac patients, either or not on GFD, to mineral metabolism derangement. Fornari et al. [27] found high levels of circulating IL-1β and IL-6 in untreated celiac patients and a reduction after GFD. In the same study, treatment produced an increase in IL-1 receptor antagonist levels which were normal at baseline evaluation, while serum levels of IL-6 negatively correlated with BMD. These findings suggest that these cytokines might have a role in the bone homeostasis during CD. In a review paper, Tilg et al. [28] pointed out the involvement of TNF-α and IFN-γ in bone remodeling, suggesting that their enhanced production and releasing during chronic inflammation is associated with increased bone loss.

Insights on the molecular mechanisms regulating osteoclast formation and activation progressed a lot in the past 15 years, with the identification of the receptor activator of nuclear factor kappa B/receptor activator of nuclear factor kappa B-ligand (RANK/RANKL) signaling system as well as the discovering of osteoprotegerin (OPG), a protein that appeared to protect from excessive bone reabsorption. Bone homeostasis is reached by a dynamic balance between bone reabsorbing activity performed by RANKL and the effects of its natural decoy receptor OPG. Fiore et al. [29] demonstrated that OPG/RANKL ratio was significantly lower in celiac patients with recovery of intestinal mucosa than in healthy controls and that positively correlated with low BMD.

In a brief paper by Riches et al. [30], autoantibodies against OPG were detected in a man with celiac disease who presented with severe osteoporosis and high bone turnover. Authors demonstrated that these autoantibodies had the potential to block the inhibitory effect of OPG on RANKL, and this led to the hypothesis that they may play a role in the development of bone derangement. In the same paper, circulating autoantibodies against OPG were detected in three among 15 additional patients with CD and low BMD, while there was no evidence of them in serum specimens from 10 healthy controls and 14 patients with autoimmune hypothyroidism. If these CD patients were or were not on GFD was not indicated by the authors, and data on duodenal mucosa histology were not provided. If circulating autoantibodies against OPG play a role in the pathogenesis of bone derangement in patients with CD, and to what extent, remains to be established. Indeed, in a more recent study, no evidence of these antibodies was found in the serum of 30 celiac patients on GFD independent of BMD, duodenal histology, and HLA status [31].

2.1.4. Diet. Naturally gluten-free products are often low in B vitamins, calcium, vitamin D, iron, zinc, magnesium, and fiber. On the other hand, few gluten-free products are enriched or fortified. Bardella et al. [32], in evaluating nutritional status and body composition of 71 adult celiac patients who adhered to GFD and displayed normal histological findings at repeat duodenal biopsy, demonstrated that BMD of adulthood diagnosed patients was significantly lower than controls. In this group, female patients showed a nutritional unbalanced diet with higher percentage of energy as fat and lower percentage of energy as carbohydrates, thus concluding that dietary advice in celiac patients other than gluten withdrawal seems to be necessary in terms of the choice and composition of foods, in order to prevent complications due to malnutrition. A dietician must be part of the health care team to monitor the patient's nutritional status and compliance on a balanced diet.

Kinsey et al. [33] described a mean daily calcium intake below the recommended 1500 mg per day and an impaired intake of vitamin D in 92% and 62%, respectively, among 106 celiac patients on GFD who participated in a dietary survey.

The real impact of vitamin D deficiency in CD is not well established at date. While Bai et al. [6] observed amelioration of BMD in celiac patients receiving calcium and vitamin D supplements compared to GFD only, Ciacci et al. [34] did not find any additional benefit from such supplementation. In a randomized prospective study, Caraceni et al. [35] evaluated BMD at baseline and after 1 year GFD in two groups of celiac patients, one receiving vitamin D orally and one who did not. No significant differences in BMD levels were found in either groups, thus suggesting a non major role for vitamin D deficiency in this setting.

2.2. Bone Metabolism in Children. During childhood and early adulthood, bone formation generally equals bone resorption, favouring the maintenance of a constant bone mass. The most rapid gain in bone mass occurs during adolescence with bone mineral accretion accelerating dramatically along with the onset of puberty, while a less consistent fraction is subsequently acquired between the ages of 20 and 30 years. If normal peak bone mass is not achieved during those critical early years, subject is at higher risk for developing osteoporosis; thus, the amount of bone accrued during the pediatric years is an important predictor of an individual's future resistance to fractures [36].

2.2.1. Malabsorption. During childhood, villous atrophy due to mucosal damage sustained by CD impairs intestinal absorption of nutrients, including the amount of calcium needed for bone accruement. Abnormal bone formation in children is an important problem for paediatricians because skeletal derangement consequences on growth are often of great importance as well as irreversible. Tau et al. [37] observed that 93% of children who started treatment before the age of 4 years reached normal spine BMD values, compared to 50% of those who were older at the time of diagnosis and gluten withdrawal. So, it can be concluded that individuals with short-term exposure to gluten are more likely to normalize their bone alterations, as a result of an optimal restoration of intestinal mucosal damage. Nevertheless, celiac children on diet for less than 12 months displayed significantly lower BMD than those on diet for more than 24 months [38].

2.2.2. PTH and Hormonal Disorders. Recent data demonstrated that bone remodeling is under endocrine control; thus, a peculiar interest for pediatricians is represented by the role of hormones and specific growth factors in the mediation of bone turnover. Secondary hyperparathyroidism could be found also in celiac children in response to hypocalcemia. In a study by Zanchi et al. [39], PTH serum concentration was higher in children with CD than in control subjects but normalized after six months GFD. Conversely, normal serum PTH levels were found in celiac children at the time of diagnosis and during the followup period by Barera et al. [40] suggesting that an increased availability of calcium in younger patients than adults may prevent hypocalcemia and secondary hyperparathyroidism. During infancy and adolescence, GH stimulates growth and sexual development as well as increasing muscle mass and the formation of bone tissue. GH deficiency was found in children with CD referred for short stature and showing no catch-up growth after 1-year GFD [41]. Since growth hormone (GH) secretion may significantly affect BMD in children, DXA scans in this setting should be evaluated with caution to avoid the risk of overestimating bone damage before treating GH deficiency. In this situation, replacement of GH therapy should be considered given the great impact of such a deficiency on the growth process. Insulin growth factor 1 (IGF-1) is essential for bone longitudinal growth; it plays a role in trabecular and cortical bone formation, and its relative deficiency may result in reduction in skeletal longitudinal growth. Federico et al. [42] evaluated IGF-1 and its binding proteins in 14 children with celiac disease, either before or after a 6-month gluten-free diet, and described a reduction of blood levels of IGF-1 and growth hormone-binding proteins during the active phase of CD which disappeared during the GFD. Also Jansson et al. [43] described a decrease of IGF-1 and its binding proteins in 54 celiac children who participated in a 4-week gluten challenge, and these findings independently correlated with weight change and small intestinal inflammation.

Another factor affecting bone remodeling in young celiac patients is the hormone leptin, the lack of which could be related to growth and puberty anomalies. Indeed, it is involved in a regulatory loop that appears to explain the protective effect of obesity on bone mass in humans. Leptinaemia levels were found to be low and to significantly increase after GFD in patients with severe intestinal atrophy [44].

2.2.3. Proinflammatory Cytokines. Garrote et al. [45] studied the complicated cytokine network involved in the pathogenesis of CD in childhood and described a particular amount of IFN-γ in the intestinal mucosa along with an increased production of IL-15, IL-18, and IL-21 linked to gluten intake. Also, Mora [46] in a review paper article speculated that increased production of inflammatory cytokines may disrupt bone metabolism equilibrium in children and adolescents with CD. Studies on the relationship between increased pro-inflammatory cytokines and bone alteration in children are scanty. Nevertheless, available findings suggest that the inflammatory pathway is involved in the development of bone impairment in celiac children as it is in adulthood diagnosed patients.

2.2.4. Diet. Monitoring dietary compliance is important to ensure appropriate bone mass accrual throughout childhood and puberty in CD patients. Adherence to a strict GFD worsens the already nutritionally unbalanced diet of adolescents, increasing elevated protein and lipid consumption despite a low carbohydrate intake [47]. Several dietary surveys observed an inadequate calcium intake among children and adolescents on GFD although the relationship between a given serum vitamin D levels and health outcomes such

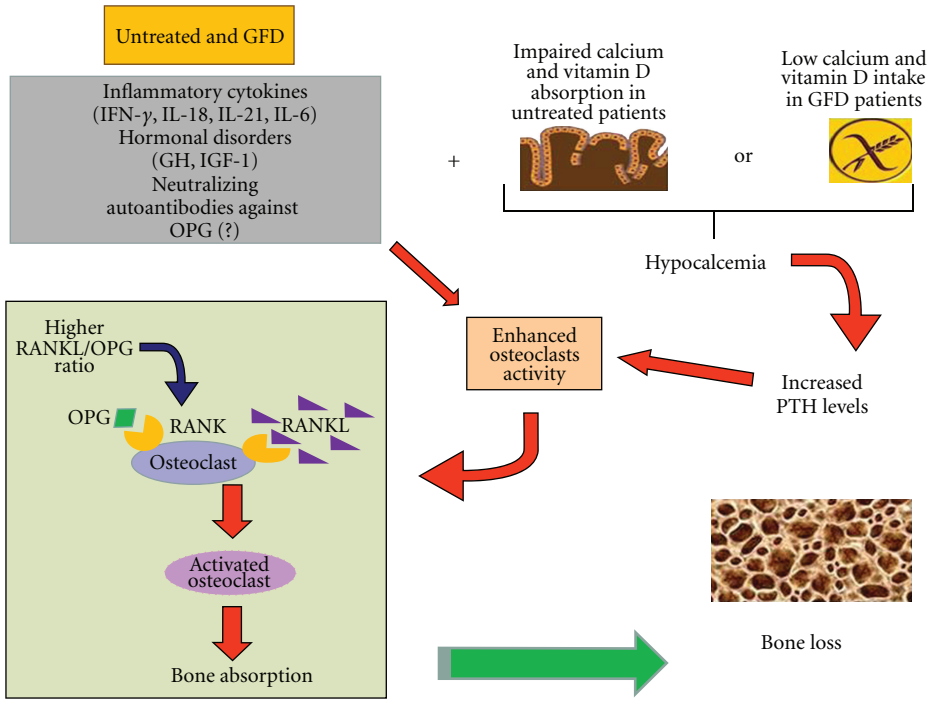

Figure 1: Mechanisms involved in the pathogenesis of bone derangement in celiac disease. GFD: gluten-free diet; IFNγ: interferon-gamma; IL: interleukin; IGF-1: insulin growth factor-1; GH: growth hormone; OPG: osteoprotegerin; RANK/RANKL: receptor activator of nuclear factor kappa B/receptor activator of nuclear factor kappa B-ligand.

as peak bone mass and fracture risk in CD children is still unclear. Vitamin D deficiency may have affected bone matrix mineralization at diagnosis due to impaired mucosal absorption even though suboptimal vitamin D and K serum levels have been found in these patients even one year after GFD [48]. Blazina et al. [49] showed that in children and adolescent, who strictly adhered to GFD and did not display low BMD, calcium intake and vitamin D levels were below recommendations. Therefore, efforts should be made to ensure an adequate calcium intake and vitamin D supplementation in this setting.

Mechanisms involved in the pathogenesis of bone derangement in CD are reported in Figure 1.

3. Clinical Aspects of Low BMD in CD

3.1. Screening for Osteoporosis in Adults. Considering that an impaired bone mass is described in both symptomatic and asymptomatic CD patients, the question arises about which patients should undergo bone mass evaluation. Despite the high prevalence of bone demineralization in CD, there is still not a consensus about the timing to perform densitometric studies. In women, postmenopausal DXA is more sensitive for detecting osteoporosis, but it could lead to a delayed diagnosis in order to achieve a bone density gain with a proper treatment. At this regard, a screening DXA at diagnosis may detect an important bone involvement allowing an early management of the disease. However, Lewis and Scott [50] in the clinical application of these guidelines in a district general hospital found a low percentage of osteoporosis in newly diagnosed celiac women who underwent DXA scan. Furthermore, data show that CD-associated low BMD responds to GFD with gradual increase of bone mineralization. In particular, a five-year follow-up study by Kemppainen et al. [51] showed a significant improvement in BMD, mostly occurring in the first year from gluten withdrawal. These findings suggest that referring patients to DXA at diagnosis of CD may overestimate the bone involvement with the risk of overtreating patients who may actually benefit of GFD alone.

3.2. Screening for Osteoporosis in Children. According to some authors, the BMD screening question in CD patients must be addressed differently in childhood. Zanchi et al. [39] detected 18% osteopenia at DXA scan in 54 untreated children and demonstrated bone improvement after 6-month GFD, concluding that an expensive study of bone metabolism is not necessary in children with CD shortly exposed to gluten. On the other hand, recent data show a less-than-optimal peak bone mass value even after two-year GFD in children with CD while biochemical markers not performing as useful tools to assess BMD impairment [52]. Kalayci et al. [53] conclude that at least 4 years of GFD are required for a complete recovery of bone mineralization in some childhood patients and even suggest annually evaluation of BMD to clarify whether bone loss is completely recovered. Indeed, the main concern is that an altered bone development during childhood can affect final growth of the child. In this context, measurement of BMD should be included in the routine management of such children

in order to implement appropriate treatment strategies and prevent long-term complications associated with poor bone health.

An additional point to discuss refers to the method for assessing bone health in childhood. Indeed, there is a debate whether DXA is an appropriate tool for studying BMD in children. Gafni and Baron [54] analyzed 34 children diagnosed with low BMD by means of DXA and found at least one error in interpretation in the 88% of the scans. The most frequent mistake was due to the use of *T*-score, that is, a standard deviation (SD) score referring to a comparison with young adults, instead of *z*-score, which indicates the difference in number of SDs between the mean BMD value of the individual and a group of people of the same sex and age. After correcting for these errors, 53% displayed normal BMD, and then half of the study population underwent a revision of their measurement. Therefore, physicians who engage DXA evaluations in children should be aware of these devices potentially leading to misdiagnosis.

3.3. Risk of Fracture. A special concern arises from the risk of fracture associated with bone demineralization in CD. Given that few studies addressed the actual fracture risk in this setting, the clinical impact of reduced BMD in CD is not well established. Furthermore, as assessed by Marshall et al. [55] in a meta-analysis of prospective cohort studies, the predictive value of DXA is not suitable enough to accurately identify subjects who will sustain fractures.

Sánchez et al. [56] evaluated the incidence and risk of peripheral fractures before and after diagnosis of CD in a cohort of 265 patients compared to a cohort of 530 age- and sex-matched controls. The CD group displayed significantly higher incidence rate and risk of peripheral fracture before diagnosis, particularly in men. The fracture risk was reduced after treatment and comparable results between the CD cohort and control group in both sexes. Jafri et al. [57] performed a population-based study in Olmsted County residents and investigated 83 celiac patients diagnosed between 1950 and 2002 and 166 gender and age-matched controls for fracture histories. A total of 39 (47%) cases had one or more fractures, with 40% occurring prior to their diagnosis date, compared to 45 (27%) controls. By means of a stratified proportional hazards model with comparable duration of follow-up in the two groups, the relative risk of having a fracture after the index date was greater in celiac patients than in their matched controls, concluding that not only fracture risk is elevated in CD, but this condition persists after the diagnosis. Thomason et al. [58] performed a large survey of patients with CD and found that 82 of 244 (35%) celiac patients and 53 of 161 (33%) age- and sex-matched healthy controls reported one or more fractures in their medical history. Accordingly, in a larger population-based case-control study which involved 1021 celiac patients, Vestergaard and Mosekilde [59] did not found a significant increase in fracture risk either before or after diagnosis of CD. Nevertheless, it must be taken into account the slight, even though not significant, increase in the risk registered in both studies, which might suggest a limitation of the study design in order to demonstrate a statistical significance rather than the absence of an association. Indeed, the sample size and the power of the study depend on the assumed fracture rate in the control population, which is different between studies. As highlighted by Walters and van Heel [60], femoral neck fractures have a population incidence of less than 1% in 65-years-old subjects but approaching 20% by the age of 90 years. However, in the study performed by Thomason et al., [58] only about one-third of individuals aged over 65 years. Therefore, approximately 400 cases and controls would be needed in a prospective study to detect a 50% increase in risk with a range from 20% to 30% and a 90% power. Findings are summarized in Table 3.

Table 3: Risk of fracture in celiac disease.

Authors	Comments
Marshall et al., 1996 [55]	DXA assessment does not accurately predict fracture risk
Vestergaard and Mosekilde, 2002 [59]	No differences before and after diagnosis of CD
Thomason et al., 2003 [58]	No difference in fracture history between CD and control patients
Jafri et al., 2008 [57]	Fracture risk is higher in CD patients, even on GFD
Sanchez et al., 2011 [56]	Fracture risk is comparable between CD and control patients

DXA: dual-energy X-ray absorptiometry; CD: celiac disease; GFD: gluten-free diet.

On the basis of current data, a correct conclusion might be that an increased fracture risk in CD cannot be excluded, but the clinical impact of this occurrence is relatively minor in celiac patients considered as a whole population.

4. Treatment of Bone Loss in CD

In children with CD, GFD is currently the first-choice therapy since it restores the intestinal malabsorption and therefore provides an improvement in bone mineralization process. This has been shown by Kavak et al. [61] in 28 childhood CD patients after one-year GFD who got mean BMD values comparable to those of healthy control subjects. Accordingly, Molteni et al. [62] demonstrated no significant differences in BMD between 22 patients treated from childhood and healthy sex- and age-matched controls, suggesting a long-term protective role for GFD when strictly followed since early age. Similar findings have been reported by Barera et al. [63] in a longitudinal study enrolling 20 patients (mean age: 10.12 ± 3.07 years) where DXA-assessed BMD at diagnosis has been found lower than in controls but became comparable one year after GFD. The beneficial impact of GFD on bone health has been confirmed by Cellier et al. [64] demonstrating that patients diagnosed in childhood and who had resumed normal diet in adolescence displayed bone complications in adult life.

In CD patients diagnosed during adulthood, GFD is still considered to play a major role in bone health, even if it is not effective in completely reversing bone derangement by itself. McFarlane et al. [65] detected a significant gain in

BMD after a 12-month GFD period in 21 newly diagnosed adult CD patients, even though there was still a lower BMD than in healthy controls, suggesting that there may be long-term impairment of bone mineralization in some otherwise healthy celiac patients who strictly adhere to a GFD. The effect of one-year GFD on bone health has been evaluated in the study by Sategna-Guidetti et al. [8] in 86 newly diagnosed adult patients where a significant improvement of lumbar spine and femoral neck mean BMD values has been demonstrated in 83.7% patients.

Few studies tested calcium and vitamin D supplementation in adult celiac patients, and current data did not provide evidence for additional benefits to GFD. In some special situations, such as osteoporosis detected in celiac postmenopausal women, it could be useful to begin a treatment with hormone replacement therapy or bisphosphonates (antiresorption agents). In addition, education on the importance of lifestyle changes, such as regular exercise, smoking cessation, and excessive alcohol intake, should be provided [66].

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Review Article

Celiac Disease and Dermatologic Manifestations: Many Skin Clue to Unfold Gluten-Sensitive Enteropathy

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Cutaneous manifestations of intestinal diseases are increasingly reported both in the adult and in the children, and this association cannot longer be considered a simple random. Besides the well-known association between celiac disease (CD) and dermatitis herpetiformis (DH), considered as the cutaneous manifestation of gluten-dependent enteropathy, is more frequently reported also the association with other mucocutaneous diseases. Among these there are both autoimmune, allergic, and inflammatory diseases, but also a more heterogeneous group called miscellaneous. The knowledge about pathogenic, epidemiological, clinical, and diagnostic aspects of CD is increasing in recent years as well as those about DH, but some aspects still remain to be defined, in particular the possible pathogenetic mechanisms involved in the association between both CD and DH and CD and other immunological skin diseases. The aim of this paper is to describe the skin diseases frequently associated with CD, distinguishing them from those which have a relationship probably just coincidental.

1. Introduction

In recent years, the knowledge about pathogenic, epidemiological, clinical, and diagnostic aspects of celiac disease (CD) has rapidly increased.

CD, also known as celiac sprue or gluten-sensitive enteropathy, can be defined as a permanent intolerance to wheat gliadins and other cereal prolamins in the small bowel mucosa in genetically susceptible individuals. The main expression of the disorder consists in characteristic, though not specific, small intestine lesions that impair nutrient absorption and improve upon withdrawal of the responsible cereals. Nevertheless, the clinical presentation of the disease can often be misleading as highly variable from one patient to another, leading to frequent delays in diagnosis [1], thus it is important to take into account both the distinction between classical (typical), subclinical (atypical or mono-symptomatic), silent (asymptomatic) and potential/latent CD [2] as well as the extraintestinal manifestations of the disease and/or the different associated disorders affecting different organs and systems recently classified as autoimmune, idiopathic, chromosomal, and miscellaneous. Among them there are many mucocutaneous diseases. In 2006, Humbert et al. proposed to classify skin diseases associated with CD in those improved by gluten-free diet and those occasionally associated with CD, dividing them into four categories: autoimmune, allergic, inflammatory, and miscellaneous [3] (Table 1).

In the present paper, the main features of the skin and oral diseases with a proven association with CD and those that improve after a gluten free-diet were described. Moreover, other skin conditions sporadically associated with CD as well as dermatologic manifestation secondary to nutritional deficiencies due to the enteropathy were briefly reported.

2. Dermatitis Herpetiformis

The most important skin disease closely associated with CD is dermatitis herpetiformis (DH), currently considered as

Table 1: Skin diseases associated with CD (adapted from Humbert et al. [3].

	Proved association	Improvement in skin disease by gluten free-diet or/and presence of serologic markers in several data	Fortuitous association (sporadic cases reports)
Autoimmune diseases	Dermatitis herpetiformis	Alopecia areata Cutaneous vasculitis	IgA linear dermatosis Dermatomyositis Vitiligo Lupus erythematosus Lichen sclerosous
Allergic diseases		Urticaria Atopic dermatitis	Prurigo nodularis
Inflammatory diseases		Psoriasis	Palmoplantar pustolosis Pytiriasis rubra pilaris Erythroderma
Miscellaneous diseases		Oral mucosa Chronic ulcerative stomatitis	Necrolytic migratory erythema Cutaneous amyloidosis Annular erythema Partial lipodystrophy Generalized acquired cutis laxa Ichthyosis Transverse leukonychia

the cutaneous manifestation of gluten-dependent enteropathy. DH, initially described by Louis Duhring in 1983 [4], is considered an autoimmune skin disease with an estimated prevalence range from 1,2 to 39,2 per 100.000 and an incidence range of 0,4 to 2,6 per 100.000 per year with geographical variability. Males have a higher prevalence of DH [5]. In fact, most population-based studies to date have found male-to-female ratios ranging from 1,5 : 1 to 2 : 1 [6]. Interestingly, the opposite has been shown about gender prevalence of CD, with female-to-male ratios ranging from 2 : 1 to 4 : 1. The time of onset of the disease is variable. Cases of childhood DH are currently more often reported than in the past, but the average age at presentation varies from 30 to 40 years old [7, 8]. A recent epidemiological study conducted by Salmi et al. [9] in Finland reported some interesting results about the increasingly rarity of DH. Although the rates of incidence and prevalence of DH, in the Finnish population in the thirty years between 1980 and 2009, were higher than those of previous studies conducted elsewhere, in the course of time there was a downward trend especially in the 90s. In particular, the estimated prevalence rate was 75,3 per 100000, while annual incidence rates were respectively 5,2 per 100000 in 1980–1989, 2,9 per 100000 in 1990–1999 and 2,7 per 100000 in 2000–2009, with a decrease in incidence rate between the first and second 10-year period that was statistically significant. In the study of Salmi et al. [9] emerged a ratio between DH and CD of 1 : 8, that resulted lower than 1 : 5 showed in previous studies [10]. Theoretically, the risk of a celiac patient to develop DH remains high, but, being the diagnosis of the enteropathy and therefore the adoption of gluten-free diet ever earlier, the risk of DH is drastically reduced [9] as postulated also by Fry [11].

DH lesions show a typical polymorphism consisting of erythema, urticarial plaques, papules, grouped vesicles and blisters associated with intense itch and therefore followed by erosions, excoriations, and hyperpigmentation (Figure 1). In addition to the morphology, also the symmetrical distribution of the lesions on the extensor surfaces of the upper and lower extremities, elbows, knees, scalp, nuchal area, and buttocks is considered a hallmark of the disease. At times face and groins may be involved. DH is rarely observed in darker-skinned individuals [12, 13]; however, there were no significant clinical differences compared to those North European.

Since 1971, sporadic cases of DH presenting as palmoplantar purpura were reported. This uncommon skin manifestation is usually observed in the children, but a number of adult cases have been described. [14–16]

Since clinical presentation of DH is often atypical, especially in early and later stages in which prevailing scratching lesions, this diagnosis may not come to mind. DH must be differentiated from atopic dermatitis, scabies, papular urticaria, and impetigo in children, whereas eczema, other autoimmune blistering diseases (especially linear IgA bullous disease and bullous pemphigoid), prurigo nodularis, urticaria, and erythema multiforme should be considered in adults [17].

The diagnosis of DH is based on physical examination, histopathology, immunofluorescence studies, and serologic testing.

Routine histopathology of lesional skin of DH, that should ideally contain an intact vesicle or should be taken in the vicinity of early blisters [18], can be evocative, but not diagnostic, and nonspecific. Furthermore, the lesions present characteristic histopathological changes, in fact the initial inflammatory event is variable edema in the papillary dermis with discrete subepidermal vacuolar alteration and neutrophils along the dermal-epidermal junction. As the lesion develops, neutrophils, to a lesser extent eosinophils, and fibrin accumulate within the dermal papillae and form microabscesses. These become confluent resulting in a subepidermal blister. In early stages of the disease, the inflammatory infiltrate contains mostly neutrophils, but in later stages, variable numbers of eosinophils can be present [19].

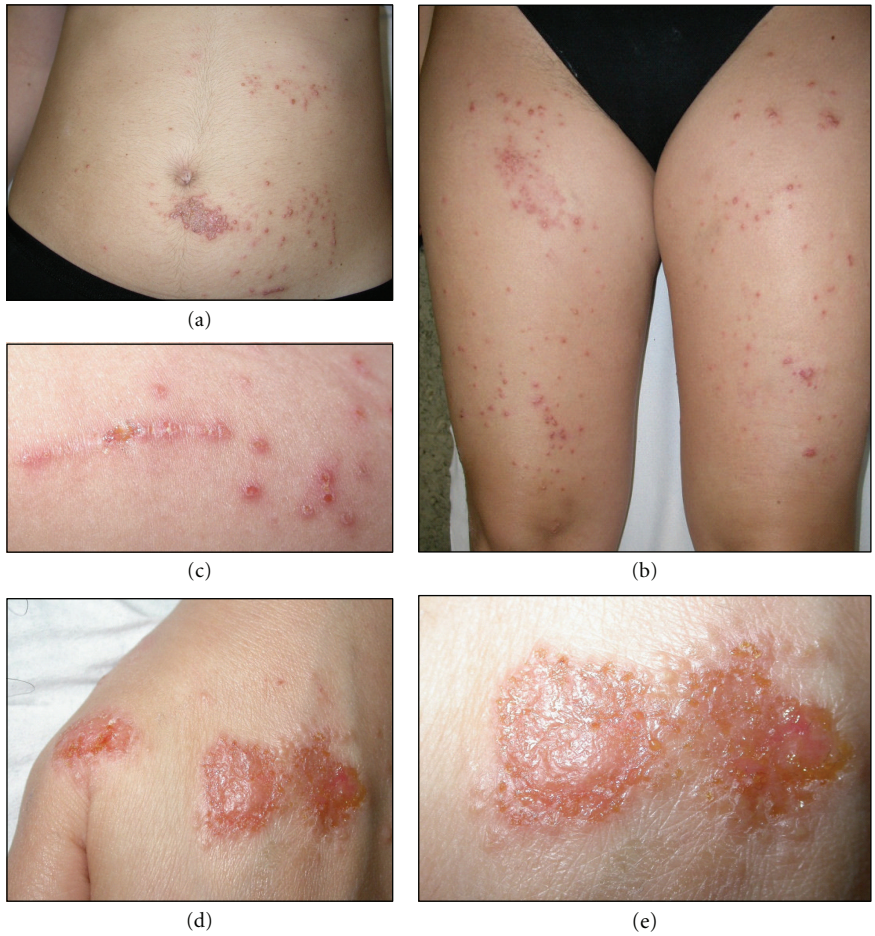

Figure 1: Erythematous, popular, and vesiculosus lesions in a patient with DH.

However, a prevalent lymphocytic infiltrate was also reported by Warren et al. [20] probably corresponding to a later stage of the disease.

However, direct immunofluorescence (DIF) on perilesional skin should be considered the gold standard for the diagnosis [21, 22].

In particular, two different patterns of DIF are possible: (a) granular deposits in the dermal papillae and (b) granular deposits along the basement membrane. Sometimes, a combination of both patterns, consisting in granular IgA deposition along the basement membrane with accentuation at the tips of the dermal papillae, may be present [23, 24]. Recently Ko et al. suggested the existence of a third different pattern of IgA deposition at DIF, the fibrillar pattern, that may be related to a clinical variant of DH [25].

Also serologic tests, and in particular IgA antitissue transglutaminase antibodies (anti-tTG) and IgA endomysial autoantibodies (EMA), have become relatively sensitive and specific tools for detection of gluten-sensitive diseases and therefore of DH in subjects on a diet free. Other serologic tests for the diagnosis of DH include the detection of antibodies directed to epidermal TG (eTG), that is currently considered the key autoantigen in DH, as well as antideamidated gliadin peptides antibodies (IgA and IgG), that are particularly reliable in children under two years old, and antibodies against to the covalent complex tTG-deamidated gliadin peptides, that was coined as neoepitope [26, 27]. Currently, the diagnosis of CD in patients also affected by DH not requires further investigation because skin disease is sufficient for diagnosis of CD [28].

To date, the first-line therapy of DH, as well as CD, is gluten-free diet, that should not be considered as a mere symptomatic approach and therefore continue without interruption even after clinical remission [29]. Generally, several months are necessary to obtain the control of the skin disease. For this reason, other treatment may be used as symptomatic agents such as dapsone, sulfasalazine and sulphamethoxypyridazine, topical potent or very-potent corticosteroids, and antihistamines.

Since 1950, when the first report on successful use of dapsone in the treatment of DH was published [30], dapsone became the best tolerated symptomatic pharmacologic therapy for DH in both adults and children. In particular, the anti-inflammatory properties of this drug are linked to inhibition of neutrophil recruitment and local neutrophil- and eosinophil-mediated tissue injury.

Dapsone represents a valid therapeutic option during the 1- to 2-year period until the GFD is effective; dosages of 1/mg/kg/day can control itching and blister development. The commonest side effect of dapsone is haemolysis and

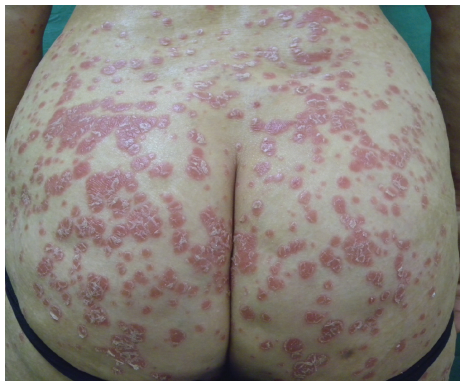

Figure 2: Erythematous scaly lesions of the buttocks in a patient affected by psoriasis.

patients should be seen within 2 weeks after starting the drug as haemolysis may be acute in some individuals [17].

Sulfasalazine and sulphamethoxypyridazine might provide an effective alternative to dapsone especially when it fails to control the disease or the therapy is complicated by adverse events [17].

3. Psoriasis

Among the inflammatory skin diseases improved by gluten-free diet, psoriasis is one of the most important. Psoriasis is a common chronic relapsing inflammatory disease of the skin, which affects about 2% of general population and characterized by scaling, erythema, and less commonly postulation (Figure 2). Some patients have affected nails and joints (psoriatic arthritis) with an obvious decline in quality of life [31].

Psoriasis is an immunological disease with an important genetic predisposition linked to HLA-Cw*0602 [32], which is characterized by hyperproliferation of keratinocytes mediated by T cells [33]. In particular, Th1 and Th17 lymphocytes contribute to the pathogenesis of psoriasis through the release of inflammatory cytokines that promote further recruitment of immune cells, keratinocyte proliferation, and sustained inflammation. The inflammatory environment seems to be amplified due to the plasticity of T regulatory cells [34], that can convert into IL-17 producing cells. Moreover genetic, experimental and therapeutic evidences have highlighted a central role for the innate immune system in the pathogenesis of psoriasis [35].

The pivotal role of immune system in psoriasis pathophysiology is also confirmed by the frequent association with other immunological diseases.

The treatment of psoriasis is often difficult, although CD patients usually show an improvement only adopting the gluten-free diet, as stated above, and then suggesting pathogenetic differences compared to nonceliac-psoriatic patients. About the association between P and CD, we must consider a recent cohort study developed by Ludvingsson et al. that showed an increased risk of psoriasis both before and after CD diagnosis. Specifically, they showed that the absolute risk of future psoriasis in patients with CD was 135/100,000 person-years, with an excess risk of 57/100,000. The hazard ratio (HR) for psoriasis remained around 1.7 also when they excluded the first year of followup. Even 5 years after CD diagnosis we did detect more than 60% increased risk for psoriasis in patients with CD [36]. Several studies suggested a correlation between psoriasis and CD [37, 38], showing an improvement in psoriatic skin lesions after 3–6 months of gluten-free diet without other pharmacological approaches [39, 40]. However, at present the relationship between CD and psoriasis remains controversial since there are few data available in the literature, and this association is considered to be coincidental by some authors [41–43]. To our knowledge, no epidemiological studies are currently available demonstrating the prevalence of psoriasis in celiac patients. In 2001, Ojetti et al. showed a prevalence of CD of 4,34% in 92 psoriatic patients [37], while Zamani et al. denied the increase prevalence of CD in Iranian psoriatic patients with respect to general population as the estimated prevalence was 0,3% [44]. However, in 2009, a new study by Birkenfeld et al. confirmed the increased prevalence of CD also in Asian population affected by psoriasis with a prevalence rate varying from 0 to 29% against 0–11% of controls [45]. Finally, the most recent study of Montesu et al. showed a celiac prevalence of 2% in patients with psoriasis, confirming an increase than in the general population [46].

The mechanisms implicated in the possible association between CD and psoriasis, and consequently the effect of gluten-free diet on psoriatic skin lesions are currently not known. Three different hypotheses have been proposed:

(1) abnormal small intestinal permeability, frequently present both in psoriatic [47] and in CD patients [48], could be a triggering factor between CD and psoriasis;

(2) T cells play an important role in the pathogenesis of both psoriasis and CD. An increased number of T CD4+ cells in the blood, in the dermis, and in the epidermis of psoriatic patients have been documented [49]. In CD patients, gliadin induces a sensitization of T CD4+ cells [50], and this may play a role in the pathogenesis of psoriatic skin lesions [51];

(3) psoriatic lesions in CD patients could be related to vitamin D deficiency, which is present both in CD [52] and in psoriasis [53, 54].

Moreover, recent observations of Troncone and Jabri [55]. suggested that psoriasis could be considered as a part of gluten sensitivity at least in a subgroup of patients. In those patients, the site of immunization against gluten may be extraintestinal and or TG is probably not the main target antigen, since 16% of patients with psoriasis have been found to present high levels of IgA and or IgG antibodies to gliadin in the absence of anti-TG antibodies, showing a significant reduction when they were put on a gluten-free diet [56].

4. Alopecia Areata

Alopecia areata (AA) is an autoimmune disease that presents as nonscarring hair loss, with a frequency ranging from 0.7%

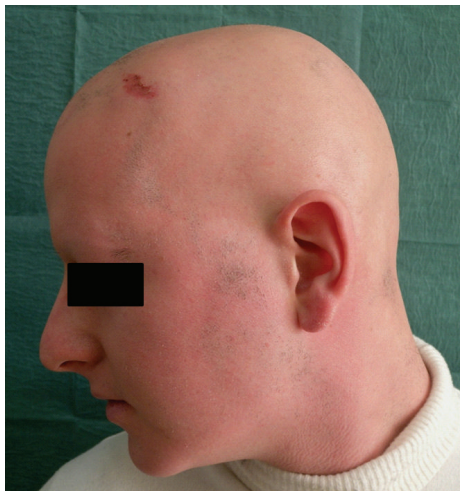

Figure 3: AA of scalp, beard, eyelashes, and eyebrows in patient affected by CD.

to 3.8% of their patients [57, 58]. Although some studies showed a significant male preponderance in adult age group, others demonstrated the opposite, indicating that AA likely affects males and females equally, as our personal clinical experience may suggest [59–61]. The disease prevalence peaks between the second and fourth decades of life [62], and pediatric reports are common accounting for 20% of all cases [63] (Figure 3).

For the first time, in 1995 Corazza et al. [64] described the association between AA and CD in 3 patients and developed a prospective screening program to ascertain whether this novel association could be real or coincidental. The estimated prevalence rate of CD in patients with AA was 1 in 85 [64], and therefore CD was included among the autoimmune diseases that may be associated with AA, in particular among those affecting the intestinal wall together with ulcerative colitis. By contrast, in 2008 Neuhausen et al. [65] considered the co-occurrence of CD and other autoimmune diseases both in celiac and their first-degree relatives in the North American population without finding an increased incidence of AA different from other autoimmune diseases such as insulin-dependent diabetes mellitus, juvenile rheumatoid arthritis/juvenile idiopathic arthritis, and hypothyroidism. Our review of the literature showed that the reported cases of association between these two conditions are few but, being often more severe variant of AA, in particular alopecia universalis, also as only clinical presentation of CD, an active search for CD using serological screening tests should be performed to diagnose the numerous cases of subclinical CD and avoid uncomfortable gastrointestinal and extraintestinal manifestations.

Although remission and recurrence may be observed during the clinical course of AA, many patients on gluten-free diet showed complete regrowth of scalp and other body hair and no further recurrence of AA at followup. The positive effects of gluten-free diet on the pattern of autoimmune conditions, such as AA, associated with CD have been attributed to a normalization of the immune response [66].

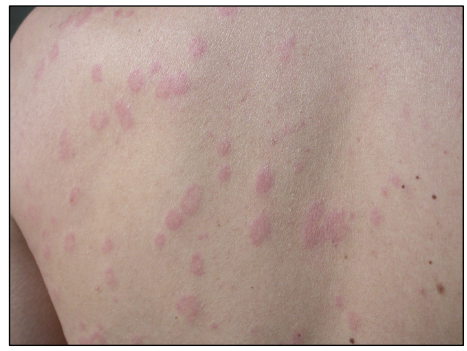

Figure 4: Pink-to-red edematous lesions, that have pale centers localized on the back of a patient affected by urticaria.

5. Chronic Urticaria

Urticaria is a common disorder, occurring in 15–25% of individuals at some point in life [67]. It is characterized by recurrent, itchy, pink-to-red edematous lesions that often have pale centers. The lesions can range in size from a few millimeters to several centimeters in diameter, and are often transient, lasting for less than 48 hours [68–71] (Figure 4). Approximately 40% of patients with urticaria also experience angioedema [68].

Urticaria is generally classified as acute (AU) or chronic (CU) depending on the duration of symptoms. AU refers to lesions that occur for less than 6 weeks, while CU to lesions that occur for more than 6 weeks; it is usually assumed that the lesions are present most days of the week [72]. Most cases of urticaria are acute; however, approximately 30% go on to become chronic. AU and CU are also distinguished by the prognosis, as AU can generally be easily managed and is associated with a good prognosis, while CU is often associated with significant morbidity and a diminished quality of life [70].

In 1987, Hautekeete et al. first described the association between CD and CU [71], although this is a matter still under debate [73]. Indeed, the relationship between the two diseases is not clear [74], but it can be speculated that autoimmunity induced by gliadin or by other unknown antigens may link CU and CD. The increased permeability of intestinal mucosa allows the passage of antigens that are responsible for CU pathogenesis by the formation of circulating immunocomplexes [75]. Both CD and urticaria are immune-mediated disorders, but they have a different pathogenesis. In fact, while CD is a Th1-mediated autoimmune response to gluten, urticaria could be supported by different mechanisms that range from Th2-driven response to allergens to Th1 autoimmunity [76]. In particular, autoimmune urticaria is related to autoantibodies against the α subunit of the high-affinity IgE receptor FcεR1 or against the α subunit of IgE. These antibodies are able to induce the mast cells degranulation and the consequent formation of anaphylatoxin [76].

However, the only epidemiologic study assessing the prevalence of CD in a population of adult idiopathic CU (ICU) patients was published in 2005 by Gabrielli et al. [73] without demonstrating an increased risk of CD in patients with ICU.

These data, obtained on a population of 80 subjects affected by ICU and 264 healthy controls, were not confirmed by larger and more detailed epidemiological studies and are in contrast not only with several case reports, but also with the results of a recent study by Confino-Cohen et al. [77]. This study considered all autoimmune diseases potentially associated to CU finding thyroid diseases the most common one and also CD the more frequent among female affected by CU. In particular, when comparing women with CU with women in the control group, the odds of having CD was 57,8, and in most cases the diagnosis of CD followed that of CU, emphasizing that a screening through the determination of the serological markers of CD in patients suffering from CU may improve the prognosis of these patients.

Furthermore, even if no meta-analysis is still available, in some cases of CU the adoption of a gluten-free diet has proven effective in controlling the skin lesions [74, 76], further confirming that CU may be a cutaneous manifestations of CD and not only a chance association.

6. Hereditary Angioneurotic Edema

Hereditary angioneurotic edema (HANE) is a rare autosomal dominant genetic disorder resulting from an inherited deficiency or dysfunction of the C1 inhibitor, a plasma protease inhibitor that regulates several proinflammatory pathways. Three phenotypic variants of HANE have been defined: type I HANE, that is characterized by a quantitative and functional deficiency of C1 inhibitor (80–85% of cases); type II HANE, which is associated with normal C1 inhibitor levels, but low function (15–20% of cases); type III HANE, that includes rare cases, usually female, in which there are no alterations of quantity and functions of C1 inhibitor and the genetic defect in most cases involves the expression of factor XII (Hageman) resulting in increased production of bradykinin [78, 79].

Clinically, HANE is characterized by recurrent episodes of angioedema, without U or pruritus, which most often affect the skin or mucosal tissues of the gastrointestinal and upper respiratory tracts. Although generally benign conditions, laryngeal involvement can rapidly lead to fatal asphyxiation if left untreated. HANE usually presents in late childhood or adolescence in otherwise healthy subjects, and a familial history is present in approximately 75% of cases. These epidemiological features are useful for the differential diagnosis with acquired angioneurotic edema (AANE), which is not associated with a family history, and usually develops in older patients (fourth decade of life) with an underlying lymphoproliferative or autoimmune disease [80].

Cases of HANE associated with ulcerative colitis and Crohn's disease have been reported by Brickman et al. in 1986 [81] and after by Farkas et al. in 1999. In 2002, Farkas et al. first described the simultaneous occurrence of HANE and CD in a 14-year-old white male, which adopted gluten-free diet three years before following the diagnosis of CD, but represented similar clinical manifestations that was hardly ranked as HANE [82]. The knowledge and the ability to diagnose HANE is important not only for its frequent association with CD, particularly because of their confusion as Farkas et al. [83] reiterated in 2011. The aim of their study was to assess the prevalence of immunoregulatory disorders within the patient population affected by HANE, including CD, and contrary to other, CD was actually more common, with a prevalence of 3,1% in patients with HANE against that in healthy controls of 0,64%. Furthermore, according to the authors, similarities between the symptoms of HANE, and CD may cause difficulties in differential diagnosis, as well as in choosing the appropriate therapy, suggesting the screening for CD in HANE patients in whom abdominal attacks or neurological symptoms persist despite adequate management.

The classic activation pathway of the complement system plays a potential role in the immune regulation of both disorders, since C1 inhibitor is deficient in HANE and gluten is considered potent activator of the alternative pathway of the complement in CD [84]. Nevertheless, there might also be a genetically determined etiology of both diseases [85]. Complement testing is justified whenever the gastrointestinal symptoms of CD persist despite restoration of damaged mucous. Conversely, HANE unresponsive to adequate prophylaxis should prompt for complete gastrointestinal group tests [86].

In the literature, there are no data available about the effectiveness of the gluten-free diet.

7. Cutaneous Vasculitis

In the literature, there are sporadic reports about the association between cutaneous vasculitis (CV) and CD [86–88].

Vasculitis (V) is defined as inflammation directed at vessels, which compromises or destroys the vessel wall leading to haemorrhagic and/or ischaemic events. The skin is the most common involved organ, and clinical manifestations include U, infiltrative erythema, petechiae, purpura, purpuric papules, haemorrhagic vesicles and bullae, nodules, livedo racemosa, deep (punched out) ulcers, and digital gangrene. These varied morphologies are a direct reflection of size of the vessels and extent of the vascular bed affected, ranging from a V affecting few superficial, small vessels in petechial eruptions to extensive pan-dermal small-vessel V in haemorrhagic bullae to muscular vessel V in lower extremity nodules with livedo racemosa [89]. Aetiologically, vasculitis can be separated into primary V (idiopathic, including cutaneous leukocytoclastic angiitis, Wegener's granulomatosis, Churg-Strauss syndrome, and microscopic polyangiitis), secondary V (a manifestation of connective tissue diseases, infection, adverse drug eruption, or a paraneoplastic phenomenon), or incidental V (a histological finding that is the consequence of another pathological process such as traumatic ulceration or diffuse neutrophilic infiltrates) [90].

Some items may help to explain how so many different diseases can coexist, in fact leukocytoclastic V is often due to immunocomplex deposition on the vessel wall, and the antigen may be either exogenous or endogenous [91]. Therefore, increased intestinal permeability being present in CD, antigens can penetrate and form immunocomplexes, that can circulate because of the impaired phagocytic function of reticular endothelium system and be deposited in

Table 2: Dermatological manifestation secondary to nutritional deficiencies.

Zinc deficiency	Crusty-erythematous-squamous dermatitis localized to periorificial regions, genitals and flexures, associated with diffuse alopecia, stomatitis, balanitis, vulvar, and proctitis
Iron deficiency	Atrophy and dryness, itching, hair loss, atrophic glossitis, angular stomatitis, and koilonychia
Vitamin A deficiency	Pytiriasis rubra pilaris-like
Vitamin B12 and folic acid deficiency	Angular stomatitis, glossitis, and oral mucosa ulcers, hyperpigmentation
Vitamin PP deficiency	Pellagra

the skin [90]. Alternatively, an autoimmune sensitization may result because of the release of endogenous antigens from damaged small bowel mucosa [92].

Treatment of leukocytoclastic V is often difficult; however, the use of corticosteroids and mostly the adoption of gluten-free diet in patients with CD has proved of great help as reported also by Marsh and Stewart [90].

8. Atopic Dermatitis

Atopic dermatitis (AD) is a very common inflammatory skin disease in childhood, that has a large impact on the quality of life both of children and their families. In developed countries, AD is affecting 15–20% of the children [93, 94], and its cumulative incidence at the age of 6 based on the criteria of Hanifin and Rajka, determined in a recent population-based prospective birth cohort study in Denmark of 562 children, was 22.8% [95]. AD usually starts within the first 6 months of life. Remission during life occurs before the age of 15 years in 60–70% of cases, although some will relapse later. Most of the children have a family history of atopic diseases, and a high percentage of the children with AD are sensitized to food- and/or aero-allergens [96]. There is a large variability in the severity of the disease: most children have mild disease (70–84%) and are treated by general practitioners [97–99]. However, young age at onset (first year of life), coexistent respiratory allergy and urban living may be considered as factors of disease severity [100].

Genetic factors are thought to be involved in the development of AD involving several susceptibility loci.

The clinical manifestations of AD vary with age. It is often difficult to differentiate AD from other skin conditions such as scabies, contact dermatitis, seborrheic dermatitis, and also to those that we have already described among those more frequently associated with CD, such as DH and psoriasis [101].

As already mentioned above, CD is considered to arise from an inappropriate T-cell-mediated immune response against ingested gluten in genetically predisposed subjects [102] and therefore different from allergic, IgE-mediated reactions, in which the Th2-type lymphocytes are mostly involved [103]. Thus, one would hypothesize that Th1- and Th2-type immunity are present in a distinct patient population, but this is still a matter of controversy [101, 104]. In fact, some reports have suggested that allergy manifestations are more frequent in patients with CD [105], and asthma incidence is increased in celiac disease diagnosed in childhood [106]. Atopic disorders were more frequently found in children [107] and adult patients with CD and their relatives than in normal control subjects [108, 109]. Zauli et al. first showed that CD prevalence in Italian population of atopic patients was 1%, significantly higher than in general population [110]. On the contrary, one single case control study in children with CD denies the link between CD and allergy [111]. However, in 2004 Ciacci et al. considered both patients with and without malabsorption and showed that AD is about 3 times more frequent in patients with CD and 2 times more frequent in their relatives than in controls [112]. Unfortunately no data are available about efficacy of gluten-free diet in atopic patients with CD, because followup in the study conducted by Ciacci et al. was limited to 1 year and did not abate allergic manifestations, even if it cannot be excluded that a longer period of diet may have some effects [112].

9. Other CD-Associated Skin Conditions

As reported by Humbert et al. in 2006 [3], in addition to skin diseases with proven association with CD and those improved by gluten-free diet and/or with positivity of celiac serological markers, there are also fortuitous associations with other skin conditions. After a detailed review of the literature, we selected all the reported associations between CD and skin conditions. Although in none of these cases has been effectively demonstrated a pathogenetic link between the diseases, some of these associations are more common. Particularly lupus erythematosus [113], dermatomyositis [114], vitiligo [115], Behçet disease [116], linear IgA bullous dermatosis [117], and also both skin and mucosal manifestations of lichen [118, 119] are the most frequently reported, while prurigo nodularis [120], erythema nodosum [121], necrolytic migratory erythema [122], porphyria [123], cutaneous amyloidosis [124], pityriasis rubra pilaris [125], erythroderma [126], partial lipodystrophy [127], generalized acquired cutis laxa [128], ichthyosis [129], atypical mole syndrome, and congenital giant nevus [130] result very rare.

In addition to those listed above, there are also dermatological manifestations secondary to a deficiency of absorption of various nutrient in the intestine. The first and only case of pellagra associated with CD was reported in 1999 by Schattner [131], but CD patients may also present nonspecific dermatological disorders, that only a specialist can be traced to a specific vitamin or oligoelement. Therefore, in Table 2, we reported the main dermatological manifestations related to specific nutritional deficiencies, that a CD patient can develop during the course of the disease.

Finally, also oral cavity may be involved in course of CD by both dental disorders or oral mucosa manifestations. Recently, Rashid M et al. described oral and dental

manifestations of CD, consisting in enamel defects, delayed eruption, recurrent aphthous ulcers, cheilitis, and atrophic glossitis and stressed that "the diagnosis of celiac disease can sometimes be made from a smile" [132].

10. Conclusion

Despite the knowledge about pathogenic, epidemiological, clinical and diagnostic aspects of CD is rapidly increased in the recent years, the possible mechanisms involved in the association with other diseases and in particular with the dermatological ones remain still unclear. Several hypotheses have been proposed depending on the type of the association, but the most probable may involve both a genetically conditioned lack of mechanisms for the maintenance of immunological tolerance, that consequently predisposes to autoimmunity and an abnormal small intestinal permeability, which may allow the crossing of endogenous or exogenous antigens and may provoke the immunological response, vascular alterations and, lastly, vitamin and aminoacid deficiency secondary to malabsorption in patients with CD.

Besides the importance of the diagnosis of DH, that is virtually always associated to CD and can be considered a specific marker of the disease, even the identification of the other dermatological conditions associated with gluten-sensitive enteropathy could be significant, highlighting the importance of a close collaboration between gastroenterologists and dermatologists. In fact, many skin diseases reported in this paper are actually more common in the celiacs or show atypical clinical presentation often associated with resistance to standard therapies in those patients. As a consequence, we suggest the screening for CD in patients affected by psoriasis, AA, CU, HANE, and AD, especially in cases resistant to first-line therapies.

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Research Article

Health-Related Quality of Life in Children and Adolescents with Celiac Disease: From the Perspectives of Children and Parents

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Aim. To examine how celiac children and adolescents on gluten-free diet valued their health-related quality of life, and if age and severity of the disease at onset affected the children's self-valuation later in life. We also assessed the parents' valuation of their child's quality of life. *Methods*. The DISABKIDS Chronic generic measure, short versions for both children and parents, was used on 160 families with celiac disease. A paediatric gastroenterologist classified manifestations of the disease at onset retrospectively. *Results*. Age or sex did not influence the outcome. Children diagnosed before the age of five scored higher than children diagnosed later. Children diagnosed more than eight years ago scored higher than more recently diagnosed children, and children who had the classical symptoms of the disease at onset scored higher than those who had atypical symptoms or were asymptomatic. The parents valuated their children's quality of life as lower than the children did. *Conclusion*. Health-related quality of life in treated celiac children and adolescents was influenced by age at diagnosis, disease severity at onset, and years on gluten-free diet. The disagreement between child-parent valuations highlights the importance of letting the children themselves be heard about their perceived quality of life.

1. Introduction

Celiac disease (CD) is a persistent intolerance to gluten causing a mucosal damage of the small intestine in genetically susceptible individuals. It is one of the most common food-related chronic diseases and it often emerges during childhood. Genetic and environmental factors interact in the pathogenesis, and currently the only treatment is a life-long adherence to a strict gluten-free diet [1].

When a disease starts during childhood, the development, growth, self-concept, identity, and mental health of the child may be affected. Chronically ill children are more prone to physical, psychological, and social strains than healthy children, which may influence the child's health-related quality of life (HRQoL) in a negative way [2]. The problems are often more pronounced during school age, when it is pertinent for the child not to be deviant from other children [3, 4]. The gluten-free diet may cause problems for the child and its family. It can be hard for the child both to accept and comply with the strict diet. Alienation, shame, fear of eating something that contains gluten, and a feeling of being a nuisance are some of the factors related to CD [5]. A high incidence of psychological problems, for example, anxiety and depression, has been reported in CD children compliant to a strict gluten-free diet [6]. Relatives of CD patients often worry about how the person with CD will manage their everyday life and their social life [7]. Parents of children with chronic diseases often describe a large need of professional support, education, and guidance in questions concerning the child's disease [8].

There have been several studies concerning the HRQoL of adults with CD [5, 7, 9–12] but only a few studies comprise children [13–15]. In this study, we have examined how children and adolescents with CD valued their present HRQoL, and also if age, sex, and manifestation of the disease at onset affected the children's later valuation of their HRQoL. Furthermore, there are studies showing discrepancies between parents' and children's reports on the HRQoL [16, 17]; hence, we also compared the parents' valuation of their child's HRQoL with the corresponding assessment done by their child.

2. Patients and Methods

2.1. Patients. The study comprises children with treated CD and their parents, who visited the pediatric clinics in the south east of Sweden, that is, Linköping, Norrköping, Motala, and Västervik, for their annual follow-up in 2006-2007. A total of 160 families, with CD children 8–18 years of age, were asked to participate and all of them agreed. The children were administered the child's version of the questionnaire and the parents were asked to fill in the proxy version. The questionnaires were both filled in and handed in at the time of the visit at the clinic. Children with both CD and diabetes, with poor understanding of the Swedish language, or with cognitive difficulties were not included in the study. In nine of the participating families, there were two siblings with CD.

2.2. Measures. The study is a cross-sectional study with consecutive selection. The subjective health status of the children during the last four weeks was assessed using the Swedish version of the DISABKIDS Chronic generic measure (DCGM-12, short version) [18], a questionnaire where the child estimates its quality of life based on three domains: mental health, social health, and physical health. The questionnaire is constructed to address chronically ill children between 8 and 18 years of age. There is also a proxy version of the questionnaire, where the parents estimate the quality of life of their child. The DISABKIDS questionnaire is a well-validated test, $\alpha = 0.84$ (the child version) and $\alpha = 0.86$ (the proxy version) [18], and it is translated into several languages including Swedish [19]. The questionnaire is available in both a long and a short version, and the short version was used for this study.

The domain mental health contains four questions about independence, including autonomy and ability to live without restrictions due to the disease, and emotion, including anxiety, anger, and worries. The domain social health contains two questions concerning social community, including acceptance by and good relations to others, and two questions concerning social exclusion, including shame and feeling of exclusion. Two questions in the domain physical health concern functional limitations and subjective physical health status. In this domain, there are also questions concerning medical treatment, which are of no relevance for this study. A 5-graded Likert scale scores each question, where high scoring represents high HRQoL. At the analysis, each question was recoded from 1–5 points to 0–100 points, according to the user's manual for DISABKIDS.

2.3. Manifestation of Disease at Onset. The severity of the disease at onset was estimated retrospectively by an experienced paediatric gastroenterologist. The classification was done according to Fasano and Catassi [1], describing three groups of clinical presentations. Classical (typical) form means that the child had the typical celiac symptoms and signs at onset, that is, diarrhea, failure to thrive, loss of weight, great fatigue, enlarged abdomen, recurrent infections, and low serum albumin levels. Atypical form means a less pronounced onset, often with no typical gastrointestinal symptoms. Asymptomatic means that the child had no obvious symptoms and the investigation was prompted when a close relative got the diagnosis of CD. The health estimations were scored as follows: "Classical form" = 1 point, "Atypical form" = 2 points, and "Asymptomatic form" = 3 points.

3. Ethics and Statistics

Informed consent was received from all the participating parents, and the study was approved by the Research Ethics Committee at the Faculty of Health Sciences, Linköping University, Linköping, Sweden.

Since data were not normally distributed, nonparametric tests were used. For analysis of quantitative data (e.g., male/female), the Mann-Whitney U-test was used, and Wilcoxon's test was used for comparisons between paired groups (e.g., child/parents). When comparing three or more groups, the Kruskal-Wallis test was used. The relationship between variables was analyzed using Spearman correlation analysis. All analyses were performed using GraphPad Prism (version 5.0d for Mac OS X, GraphPad software, San Diego, CA), and P values equal or less than 0.05 were considered significant. If nothing else is indicated, all values are presented as median (25th percentile–75th percentile).

4. Results

The study comprises 160 children with confirmed celiac disease, 55 males and 105 females. Median age at inclusion, that is, when the questionnaire was filled in, was 13 years (range 8–18 years), and the median time since the diagnosis of CD was 10 years (range 1–17 years). The children were diagnosed between the years 1989 and 2006. A high percentage of the included cases (43%) were diagnosed between 1992 and 1996. The children were divided into three age groups: 8–11 years ($n = 42$), 12–15 years ($n = 104$), and 16–18 years ($n = 14$). The final response rate was 97.5% ($n = 156$, 54 males, 102 females) among the children and 95% ($n = 152$) among the parents. One child-questionnaire was ruined and three parents were visiting the clinic without their children, hence the loss among the children ($n = 4$). Eight adolescents visited the clinic without their parents, explaining the loss among the parents ($n = 8$). Hence, the results from comparisons between children and parents are presented from 149 child/parents pairs. Age and

Table 1: Age and sex distribution of the study population and the response rate of the questionnaires.

	Number of participating families			Response rate, *n*			
Age	Total	Female	Male	Children	Female	Male	Parents
8–11	42	25	17	41	25	16	42
12–15	104	67	37	102	65	37	100
16–18	14	13	1	13	12	1	10
Total	160	105	55	156[a]	102	54	152[b]

[a] One questionnaire was broken and three parents came to the clinic without their children.
[b] Eight adolescents visited the clinic without their parents.

sex distribution, as well as the response rate, are shown in Table 1.

4.1. Total Score. The median value of the children's total score was 92 points (85.5–96). The median values in the separate specific domains were mental health 85 points (75–95), social health 95 points (85–100), and physical health 100 points (90–100).

4.2. Sex and Age. Sex and age did not correlate with the children's HRQoL score ($P = 0.59$ and $P = 0.82$, resp.). The only difference was seen in the age group 8–11 years, in which the boys ($n = 16$) scored lower than the girls ($n = 25$) in the domain physical health, with scores of 95 (90–100) and 100 (100-100), respectively ($P = 0.05$).

4.3. Years Since Diagnosis. The years since diagnosis were weakly ($r = 0.26$) but significantly ($P < 0.001$) correlated with the children's self-assessed quality of life. Those who received their diagnosis nine or more years ago valued their HRQoL higher than those who received it more recently (1–8 years), with scores of 92 (58–96) and 90 (36–94), respectively ($P = 0.02$). This was true also in the domain mental health where the groups scored with the median of 90 (55–95) and 85 (35–90), respectively ($P = 0.01$).

4.4. Age at Diagnosis. Age at diagnosis was negatively correlated with the HRQoL score ($P < 0.001$). The children who received the diagnosis before the age of five ($n = 93$) scored higher than to those who were five years old or more ($n = 63$) at the diagnosis, with scores of 92 (88–96) and 90 (82–94), respectively ($P = 0.006$) (Figure 1).

In the domain mental health, the children diagnosed before or after five years of age scored with the median of 90 (55–95) and 85 (35–95), respectively ($P = 0.03$), and in the domain social health median 95 (90–100) and 90 (85–100), respectively ($P = 0.01$) (Figure 1).

4.5. Disease Manifestation at Onset. The children who presented with the classical form of CD ($n = 68$) valued their present HRQoL as higher than those who presented with atypical form ($n = 74$) or those who were asymptomatic ($n = 14$) with scores of 92 (88.5–97.5), 90 (84–94), and 88 (80.5–94.5), respectively, with a significant difference between the classical and the atypical group ($P = 0.03$). The median age in the three groups was 1, 7, and 7.5 years, respectively. The disease state at onset was found to be correlated with the children's total score ($P < 0.05$).

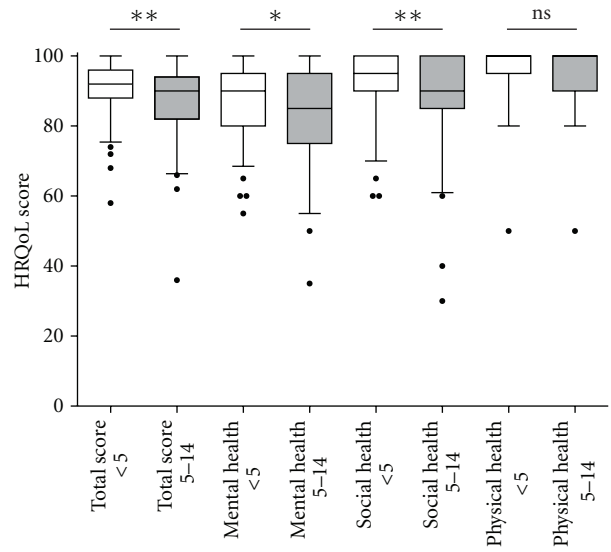

Figure 1: When assessing the health-related quality of life (HRQoL), using the DISABKIDS test, the children who received the diagnosis celiac disease before the age of five ($n = 93$) (<5, open boxes) scored higher in the total test, as well as in the domains mental and social health, as compared to children who were five years or older at the time of diagnosis ($n = 63$) (5–14, filled boxes). Box plot shows the median and 25th and 75th percentiles. Error bars represent 10th and 90th percentiles. $^{**}P < 0.01$; $^{*}P < 0.05$; ns: not significant.

4.6. Parents/Children. The parents' median total score for their children's HRQoL was 86 (80–92) while the children's median total score was 92 (84–96), and this difference was significant ($P < 0.001$), although the values were well correlated ($r = 0.43$, $P < 0.001$). The parental estimations were lower also in the specific domains: in mental health the parents' and the children's median score was 80 (75–90) and 85 (75–95) ($P = 0.003$); in social health 90 (80–95), and 95 (85–100) ($P < 0.001$); and in the domain physical health 100 (20–100) and 100 (50–100) ($P = 0.005$), respectively (Figure 2).

Age and sex of the children did not correlate with the parents' valuation of the children's HRQoL, neither did the manifestation of the disease at onset. However, there were

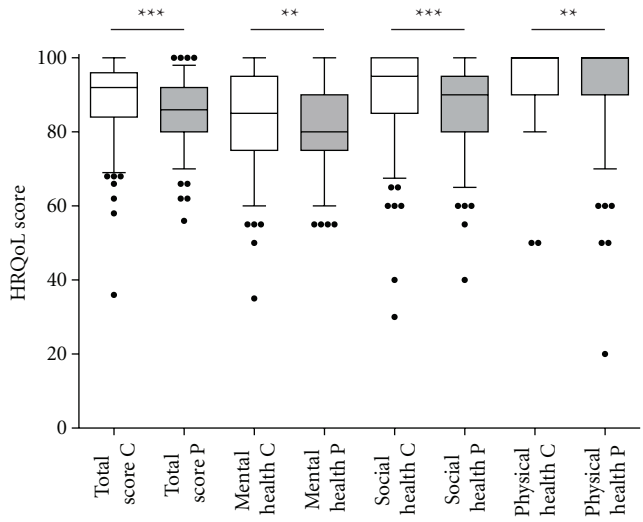

Figure 2: The parents (P, filled boxes) valued their children's health-related quality of life (HRQoL) as lower than the children themselves did (C, open boxes), both in the total score and in the three domains mental, social, and physical health. Box plot shows the median and 25th and 75th percentiles from 149 child/parents pairs. Error bars represent 10th and 90th percentiles. $^{***}P < 0.001$; $^{**}P < 0.01$.

significant differences in the estimation of the HRQoL if the child was diagnosed before or after the age of five (median 86, 82–94 and median 84, 78–90, resp.) ($P = 0.02$). There was also a weak, but significant, correlation between the parents' estimation and the duration of the disease for the child ($r = 0.18$, $P = 0.03$).

5. Discussion

In this study, we have assessed the subjective health-related quality of life in children and adolescents with treated CD, and the corresponding evaluation made by their parents. We found that the children valued their quality of life as very high, but the parents estimated their children's HRQoL as lower than their children.

The results suggest that the children, as a group, have adapted well to the disease. Indeed, in two earlier studies [14, 15], the authors claim that children with CD who keep a strict gluten-free diet experience the same high HRQoL as healthy children. While being aware that we could lower the sensitivity and specificity by not choosing a disease specific measure [20], we have used the DISABKIDS chronic generic measure, which is a well-established and validated instrument for assessing HRQoL in children with chronic diseases [18]. The instrument may be used for different diagnostic groups, and this makes comparisons possible on how distinct diseases affect children's self-estimated quality of life. In a pilot study done by the DISABKIDS group, other chronic diseases, such as asthma, arthritis, dermatitis, diabetes, cerebral palsy, cystic fibrosis, and epilepsy, were tested [18]. The mean total score for these conditions ranged between 63 and 81 points, with the cerebral palsy children scoring lowest and the asthma children highest. There were no reference values for celiac disease; hence, the present study is to best of our knowledge the first to show values for CD using this instrument. The CD children in our study scored higher than the children affected by other chronic diseases both in total score and in the three domains of the questionnaire.

Measurements of HRQoL based on life situations are difficult to perform, since both subjective and objective circumstances must be taken into consideration. It has been reported that children's compliance to a gluten-free diet was correlated with the parent's knowledge and understanding of the disease. This in turn was highly correlated with the social status of the families [21]. In the present study, neither the socioeconomic factors of the family, nor the parents' occupation, education, or the living environment have been highlighted. However, in order to elucidate the significance of different factors on the quality of life, we related the HRQoL of the children to age, sex, years since diagnosis, age at diagnosis, and the severity of the disease at onset. The results show that sex had no impact on the HRQoL, neither had age as a single factor.

Children who were diagnosed before the age of five scored better than those who were five years or older at the diagnosis. Furthermore, we noted that children who had had their disease for a long time experienced their current quality of life as higher. These results are consistent with the report from Högberg et al. [22], where children who were diagnosed before the age of four accepted their illness and the gluten-free diet better than those who were diagnosed later. The young children have probably not been accustomed to the taste of gluten-containing food, which may result in a better compliance to the gluten-free diet. There are studies showing that it may be difficult to adapt to a chronic disease during adolescence, the period of life when the needs to be like the others probably are the highest [3, 23, 24].

An additional factor influencing the children's HRQoL was the manifestation of the disease at onset. The classification into three groups was done retrospectively by an experienced paediatric gastroenterologist, thereby increasing the reliability of the assessment. The children who presented with the classical form of the disease valued their HRQoL as highest. The majority of the children in this study who were diagnosed before the age of four presented with the typical CD symptoms, for example, diarrhea, failure to thrive, loss of weight, and enlarged abdomen. Currently, the median age at diagnosis has increased, and children receive their diagnosis more often at an older age and present with more diffuse symptoms [25]. Further studies should be performed on the latter patient group, using the same instrument, in order to reveal the importance of age at diagnosis and disease severity as predictors of HRQoL later in life.

Some children in this study had extremely low scores in HRQoL (Figure 2). We cannot explain if this is due to celiac disease or due to other factors that were not assessed in this study. Yet, such low values should alert the health professionals to evaluate the need for psychological and social support.

According to Eiser and Morse [26], parents with chronically ill children are able to make a better valuation of

their child's HRQoL as compared to parents with healthy children. In the present study, the parents valued their children's HRQoL as lower than the children themselves did. This was noted both for the total quality of life and for the three domains mental, social, and physical health. Sawyer et al. [27] described how health care professionals often listen only to the parent's description of the child's problems, which may lead to a misinterpretation of the child's HRQoL by the staff and a risk for overtreatment of the child. Parents of CD children are often worried about possible complications, development of other autoimmune diseases, fertility, and heredity. They are also concerned about what the children have to endure, and what they have to abstain from, and indeed, the greatest discrepancy between children and parents in this study was seen in the domain social health. The parent's lower valuation of their children's HRQoL may also be due to the parent's sense of responsibility and concern as the basis for the valuation [27]. Many parents feel guilt, sadness, bitterness, and difficulties of coping in the everyday life when their child is diagnosed with a chronic disease. Indeed, parents in all the diagnostic groups in the pilot studies in DISABKIDS valued the children's HRQoL lower than their children did [18]. Interestingly, when assessing HRQoL in the parents of children with CD, de Lorenzo et al. [13] found an impaired self-valuation in comparison to parents of healthy children, especially in the social dimension. This suggests an impact of the diet regimen and possibly other factors on the parents and on close relatives, a suggestion that was also proposed by Sverker et al. [7].

The parent's valuation was also affected by the age of the child at the time of diagnosis. The younger the child was at onset, the better was the parent's valuation of its present HRQoL. This may be due to the fact that the youngest children also had the most severe symptoms of the disease and, hence, were the ones that most obviously benefitted from the gluten-free diet. Furthermore, parents of children who had the diagnosis for a long time tended to value their child's quality of life higher, possibly reflecting that the families were getting used to the diet regimens and all the difficulties that could come out of it.

One important limitation of the present study was the lack of a control group of healthy individuals. However, the instrument used in the study was developed to address children with chronic diseases making the use of a healthy control group difficult. Furthermore, while our study group had higher HRQoL than groups with other chronic diseases, other studies reported that children with CD generally had high values in HRQoL measurements and that the values were similar to the control groups [13, 14]. On the contrary, when assessing psychological symptoms in treated CD children and controls, Mazzone et al. [6] found signs of more depression and anxiety in the CD group, indicating an influence of the strict diet regimen on the child's psychological well-being, something that health care professionals should be aware of.

The reason for using HRQoL instruments in health care is to get a combined picture of the mental, social, and physical health of the child. This could help the health care professionals in getting a clearer view of how the children and their relatives experience chronic diseases. In the present study, it was important that both the celiac child and the parents made an estimation of the child's current HRQoL, in order to improve our knowledge of the living conditions for celiac families.

In conclusion, children who were diagnosed before the age of five and who presented with the classical form of CD scored their health-related quality of life higher. The children who have had the disease for a longer time also scored higher. The celiac children in this study scored higher than other diagnostic groups assessed with the same instrument. Notably, the parents scored significantly lower than the children when they were asked to evaluate their child's HRQoL. The disagreement between the self- and the proxy valuations highlights the importance of letting the children themselves be heard about their perceived quality of life.

Abbreviations

CD: Celiac disease
HRQoL: Health related quality of life.

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Research Article

Frequency of Celiac Disease in Adult Patients with Typical or Atypical Malabsorption Symptoms in Isfahan, Iran

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Aim. Atypical presentations of celiac disease (CD) have now been shown to be much more common than classical (typical) form. We evaluated the frequency of CD among adult patients with typical or atypical symptoms of CD. *Materials and Methods*. Patients referred to two outpatient gastroenterology clinics in Isfahan (IRAN) were categorized into those with typical or atypical symptoms of CD. IgA antitissue transglutaminase antibody was assessed and followed by duodenal biopsy. In patients for whom endoscopy was indicated (independent of the serology), duodenal biopsy was taken. Histopathological changes were assessed according to the Marsh classification. *Results*. During the study period, 151 and 173 patients with typical and atypical symptoms were evaluated (mean age = 32.8 ± 12.6 and 35.8 ± 14.8 years, 47.0% and 56.0% female, resp.). Frequency of CD in patients with typical and atypical symptoms was calculated, respectively, as 5.9% (9/151) and 1.25% (3/173) based on positive serology and pathology. The overall frequency was estimated as at least 9.2% (14/151) and 4.0% (7/173) when data of seronegative patients were also considered. *Conclusions*. CD is more frequent among patients with typical symptoms of malabsorption and these patients should undergo duodenal biopsy, irrespective of the serology. In patients with atypical symptoms, serological tests should be performed followed by endoscopic biopsy, and routine duodenal biopsy is recommended when endoscopic evaluation is indicated because of symptoms.

1. Introduction

Celiac Disease (CD), also known as gluten-sensitive enteropathy, is a genetic disorder affecting both children and adults. People with CD are unable to eat foods that contain gluten because, in these patients, gluten sets off an autoimmune reactions that cause the destruction of the small intestinal villi and leading to a malabsorption syndrome [1, 2]. While it was previously thought to be rare, epidemiological studies using sensitive and specific serological tests with biopsy verification established higher prevalence of CD (up to 1 : 100) in most countries [3–5].

Classical symptoms of CD in adults include chronic diarrhea, steatorrhea, and weight loss. Steatorrhea is associated with severe, extensive enteropathy, but it is often absent in patients whose disease is limited to the more proximal portions of the small intestine [2]. Classical symptoms of CD are present in less than 50% of the patients at presentation [1]. Abdominal discomfort and bloating are common at early presentation and often result in a mistaken diagnosis of more common gastrointestinal disorders such as irritable bowel syndrome (IBS) and dyspepsia for a long time, which contributes to a considerable delay in diagnosing CD [6, 7]. Untreated CD can be life threatening and increase the risk of certain types of cancer and lymphoma and also increase the risk of mortality compared to the general population [8]. Although there are no drugs to treat CD and there is no cure, a gluten-free diet (GFD) can lead to a normal and healthy live

and can decrease the risk of malignancy and mortality [2, 8]. Therefore, prompt diagnosis of the disease and nutritional treatment is of great value.

Despite the large epidemiological studies and screening and nutritional programs conducted in western countries, there are only a few investigations on the prevalence of CD in the general population in Asia, particularly Middle East [5, 9]. Epidemiological studies in Iran also are insufficient to provide an accurate estimation of CD among high risk or suspicious groups. Since there are few documented cases of CD in our society, it seems to be remained underdiagnosed [5].

There is still a controversy on cost-effectiveness and benefits of the population screening for CD [10, 11]. In the absence of a population screening program, targeting the screening to the certain high risk groups (case finding approach) can be an efficient use of the resources [10]. Epidemiological studies providing an estimated prevalence among different target groups (e.g., apparently healthy, suspicious CD, and high-risk groups) will enable us to establish further genetic, immunologic, and nutritional researches to control the disease. According to the wide aspects of presentation and variety of complications, and also regarding the lack of epidemiologic data on CD in Iran, we aimed to determine the prevalence of CD among patients referred with typical or atypical symptoms of malabsorption to see if routine screening of these patients is worthwhile.

2. Materials and Methods

2.1. Patients and Setting. This study was conducted between 2004 and 2005, on all patients with typical or atypical symptoms of CD referred to Poursina Hakim Research Institute (including two outpatient clinics of gastroenterology) in Isfahan, Iran. Classic or typical symptoms of CD were considered as chronic diarrhea, steatorrhea, and weigh loss. Atypical symptoms included unexplained abdominal pain, excessive gas passing, malodor stool or gas, constipation, intermittent diarrhea, bloating, and unexplained nausea or vomiting. The ethics committee of the Isfahan University of Medical Sciences approved the study and informed consent was obtained from all patients after explaining the aims and protocol.

2.2. Assessments. Data including demographics, clinical symptoms, complete past medical history, and associated disorders, and family history of CD were collected by a trained physician using a structured questionnaire. Laboratory data included thyroid function test, complete blood count (CBC), ESR, CRP, calcium, phosphor, and 3 times stool examination for all patients.

2.3. Serological Assessment for CD. The IgA antitissue transglutaminase (anti-tTG) antibody was measured for all patients using an enzyme-linked immunosorbant assay (ELIZA) technique by a commercially available kit (ORG540 A, ORGENTEC Diagnostica GmbH). The upper limit of the normal range (cut-off value) for t-TG IgA antibody, as determined by the manufacturer, was 10 u/mL. If the results was very low (<5 Au/mL), IgA level was measured to rule out IgA deficiency.

2.4. Pathological Assessment for CD. Endoscopic biopsy was recommended to all patients with typical symptoms, seropositive atypical cases, and those with IgA deficiency [1, 12]. Also, duodenal biopsy was done in seronegative patients with atypical symptoms, who had other indications of upper gastrointestinal endoscopy (due to their symptoms). Endoscopy was done with a standard 110 cm long video endoscope (EG 2940, Pentax EPM-3300), by a single gastroenterologist, during which at least four biopsy specimens were obtained from the distal part of the second portion of duodenum. The specimens were processed and stained with hematoxylin and eosin and studied under light microscopy by a gastrointestinal oriented pathologist. Histopathology was reported according to the modified Marsh classification [13]; Marsh type I: infiltrative phase with >30 lymphocytes per 100 enterocytes; Marsh II: infiltrative/hyperplastic phase; Marsh IIIA, IIIB, and IIIC: partial, subtotal, and total villous atrophy, respectively. Seropositive patients with at least Marsh I of villous atrophy and also seronegative cases with Marsh II or III of villous atrophy were considered to have CD if they had good response to GFD [12].

2.5. Statistical Analysis. The data were analyzed using SPSS software for Windows v 16.0 (SPSS Inc., Chicago, IL, USA). Comparisons were done with independent t-test or Mann-Whitney test for quantitative and Chi-square or Fisher's exact tests for qualitative data, and a P value of <0.05 was considered to be significant.

3. Results

During the study period, 151 patients with typical symptoms (mean age = 32.8 ± 12.6, 47.0% female) and 173 patients with atypical symptoms (mean age = 35.8 ± 14.8, 56.0% female) were evaluated. Comparisons of the two groups regarding demographic characteristics and symptoms are presented in Table 1. The differences between patients with typical and atypical symptoms in age and gender were not statistically significant ($P > 0.05$). The frequency of intermittent diarrhea and constipation was higher in atypical ($P < 0.05$) and fatigue/weakness in typical cases ($P < 0.001$). Duration of symptoms was longer in patients with atypical symptoms ($P < 0.05$).

3.1. Patients with Typical Symptoms for CD. In patients with typical symptoms, thyroid function test, stool exam, ESR and CBC results did not specify a diagnosis. Patients ≥ 50 years old (17 cases) underwent total colonoscopy and none of them had malignancy or inflammatory bowel disease. Family history of CD was not reported and IgA deficiency was not detected in any patient. Totally, 8.6% (13/151) of the patients with typical symptoms were seropositive for tTG-IgA, 12 patients accepted to undergo endoscopy. Histopathological studies showed Marsh IIIc in 4, Marsh IIIb in 3, and

Table 1: Patients' characteristics.

	Typical $N = 151$	Atypical $N = 173$	P
Age (year)	32.8 ± 12.6	35.8 ± 14.8	0.057*
Male/Female	80 (52.9%)/71 (47.0%)	76 (43.9%)/97 (56.0%)	0.065**
Symptoms			
Chronic Diarrhea	107 (70.8%)	—	—
Steatorrhea	40 (26.4%)	—	—
Weight Loss	64 (42.3%)	—	—
Abdominal Pain	80 (52.9%)	79 (45.6%)	0.115**
Bloating	68 (45.0%)	75 (43.3%)	0.424**
Intermittent Diarrhea	8 (5.2%)	26 (15.0%)	0.005**
Constipation	30 (19.8%)	60 (34.6%)	0.002**
Flatulence	65 (43.0%)	88 (51.4%)	0.098**
Fatigue/Weakness	56 (37.0%)	30 (17.3%)	<0.001**
Symptom Duration (Month)	36.3 (SE = 3.6)	54.7 (SE = 5.7)	0.008*

Data are presented as mean ± SD (SE) or number (%).
*Independent Sample t-Test or Mann-Whitney Test.
**Chi-Square or Fisher's Exact Tests.

Marsh I in 2 patients. As upper gastrointestinal endoscopy was offered to all patients, 40.2% (56/139) accepted this procedure. Histopathological studies among these patients showed Marsh IIIc in 1, Marsh IIIb in 2, Marsh IIIa in 3, Marsh II in 1, and Marsh I in 9 patients. GFD was started in all patients with positive serology and a biopsy result suggestive of CD and in seronegative patients with Marsh III or II. One seronegative patient with Marsh IIIc and one with Marsh II did not respond to GFD and after more evaluation including colonoscopy, the patient with Marsh IIIc was diagnosed to have Crohn' disease. Other patients responded to GFD clinically and antibody became negative after six months in seropositive cases. Therefore, the prevalence of CD in patients with typical symptoms was calculated as 5.9% (9/151) based on positive serology and confirmed pathology and the overall prevalence was estimated as at least 9.2% (14/151) when data of seronegative patients were considered, as well. Patients' characteristics are shown in Table 2.

Table 2: Patients with CD and typical/atypical symptoms.

	Typical $N = 14$	Atypical $N = 7$	P
Age, year	33.5 ± 13.0	39.2 ± 12.3	0.795*
Male/Female	6 (42.8%)/8 (57.1%)	3 (42.8%)/4 (57.1%)	0.676**
Positive serology	9 (64.2%)	3 (42.8%)	0.319**
Marsh classification			
I	2 (14.2%)	0	
II	0	5 (71.4%)	
IIIA	3 (21.4%)	2 (28.5%)	0.004**
IIIB	5 (35.7%)	0	
IIIC	4 (28.5%)	0	

Data are presented as mean ± SD (SE) or number (%).
*Independent Sample t-test or Mann-Whitney test.
**Chi-Square or Fisher's Exact Tests.

3.2. Patients with Atypical Symptoms for CD. In this group, 8 patients were diagnosed to have IgA deficiency, but none of them had CD. Totally, 2.8% (5/173) of the patients were seropositive for IgA anti-tTG, and in all of them duodenal biopsy was taken. Marsh II was shown in 3 of the patients, and 2 of them had normal histopathologic examination. As upper gastrointestinal endoscopy was offered to all patients with prolonged and unexplained symptoms, 37.5% (63/168) patients accepted this procedure. Among these patients, 2 had Marsh IIIa, 2 had Marsh II, and 6 Marsh I. GFD was started in all patients with positive serology and a biopsy result suggestive of CD and also in seronegative patients with Marsh III or II. All patients responded to GFD clinically and serology became negative in seropositive cases after six months. Finally, the prevalence of CD in patients with atypical symptoms was calculated as 1.25% (3/173) based on positive serology confirmed by pathology and the overall prevalence was estimated at least 4.0% (7/173) when data of seronegative patients were considered, as well. Patients' characteristics are shown in Table 2. The frequency of CD was higher in typical than in atypical patients (OR = 2.423, CI 95% = 0.95 to 6.17, $P = 0.046$ (one sided)).

Comparing patients with and without CD regarding presenting symptoms is presented in Table 3. Abdominal pain, diarrhea, bloating, and steatorrhea were more frequent in CD than non-CD patients ($P < 0.05$), but the differences regarding other symptoms were not statistically significant. Also, there was no significant difference between CD and non-CD cases in age or gender ($P > 0.05$).

Table 3: Comparison of symptoms between patients with and without CD.

	CD $N = 21$	Non-CD $N = 303$	P
Age (year)	32.8 ± 12.6	35.8 ± 14.8	0.057*
Male/Female	9 (42.8%)/12 (57.1%)	147 (48.5%)/156 (51.4%)	0.065**
Abdominal Pain	15 (71.4%)	144 (47.5%)	0.028**
Diarrhea	13 (61.9%)	120 (39.6%)	0.039**
Bloating	15 (71.4%)	128 (42.2%)	0.009**
Constipation	3 (14.2%)	87 (28.7%)	0.117**
Weight Loss	5 (23.8%)	59 (19.4%)	0.402**
Flatulence	9 (42.8%)	144 (47.5%)	0.427**
Fatigue/Weakness	9 (42.8%)	77 (25.4%)	0.072**
Steatorrhea	6 (28.5%)	34 (11.2%)	0.032**

Data are presented as mean ± SD (SE) or number (%).
*Independent Sample t-test or Mann-Whitney test.
**Chi-Square or Fisher's Exact Tests.

4. Discussion

Previously, CD has been considered to be very rare in the Middle East and, based on this assumption, it was not generally considered as a possibility in the differential diagnosis of patients coming with nonspecific gastrointestinal symptoms [9]. By the development of more sensitive serological tests and a higher degree of disease suspicion, a marked increase in CD prevalence and incidence has been reported in recent decade [5]. Some evidence showed that a large proportion of patients present with atypical symptoms of malabsorption that can lead to misdiagnosis for a prolonged time [6, 14]. This delay can result in higher complications of CD such as different types of cancer and organ damage. Thus, prompt diagnosis of CD is of great important and while there is still a controversy on the cost-effectiveness of population screening for CD, case finding approach is more financially viable [10]. With this approach, we attempted to determine the frequency of CD in patients presenting with typical symptoms of malabsorption and those with nonspecific gastrointestinal complaints. We found that CD is present in about 9.2% of the patients coming with typical symptoms (12.1% (13/107) of the patients with chronic diarrhea) and 4.0% of those who come with atypical symptoms of malabsorption. Other studies from Iran also reported that CD is the most common cause of chronic nonbloody diarrhea in adults and children, ranging from 6.5% to 19% [15, 16]. These results indicate that classic presentation of malabsorption, specially with chronic diarrhea, is the main presentation of CD in our society. However, we found that 4.0% of patients coming to the outpatient clinics of gastroenterology with nonspecific symptoms of CD finally were diagnosed to have CD, which is much higher than that reported from screening studies of the general population in Iran, up to 1% [5]. Dyspepsia and IBS are the most common disorders diagnosed in outpatient clinics of gastroenterology. There are some studies with case finding approach that are done in these patients. The frequency of CD is reported from 1.4% [17] to 7% [18] in people with dyspeptic complaints and from 0.4% to 11.4% in patients with IBS [19–21]. A meta-analysis showed that biopsy-confirmed CD is 4-fold more prevalent in IBS patients than the general population (Pooled odds ratio = 4.34, CI 95% = 1.78–10.6) [22]. Studies with cost-effective analyses showed that testing for CD in patients with IBS-like symptoms is acceptable when the prevalence of CD is above 1% and it is a dominant strategy when the prevalence exceeds 8% and also in those with diarrhea predominant IBS [23, 24]. In spite of this evidence, most of the studies from Iran have shown no difference between patients with IBS-like symptoms and the general population in the frequency of CD [25]. More recent studies with large sample sizes also did not find a higher frequency of CD [20] even among patients with diarrhea-predominant IBS [19]. Therefore, decision for screening of these patients must be based on the population prevalence of CD, the accuracy of serological tests in that population, and the costs of IBS treatment [23].

An important finding in our study was the low sensitivity of serology (anti-tTG IgA antibody) in detecting CD patients specially in patients presenting with atypical symptoms. IgA anti-tTG antibody is the single most efficient serological test for the diagnosis of CD [26, 27]. It is well known that IgA anti-tTG levels correlate with the degree of intestinal damage, and that values can fluctuate in patients over time [28, 29]. Serological tests help in diagnosis of CD, but the gold standard is based on pathological study. We found that about 35% of CD patients with typical symptoms are seronegative that shows the best method for diagnosing CD in these patients is a panel of serological tests and endoscopic biopsy together, which is previously recommended by other investigators [1]. In patients with non-specific gastrointestinal symptoms we found positive serology in less than half of the patients. Accordingly we recommend that diagnostic approach in such patients should be started with serological tests and when the endoscopy is indicated for evaluation of the symptoms, duodenal biopsy and evaluation for CD histopathology should be considered. During the endoscopy, the presence of features of villous atrophy (such as scalloping

of mucosal folds, absent or reduced duodenal folds, or a mosaic pattern of the mucosa) has a high negative predictive value for CD and could be helpful in decision for biopsy [30, 31]. However, such features have a very low sensitivity [31, 32] and also evidence has shown that duodenal biopsies reveal other abnormalities and could be helpful in patients with chronic diarrhea and/or abdominal pain for further following workups [33]. Therefore, we recommend routine duodenal biopsy in endoscopic evaluation of patients referring with nonspecific gastrointestinal symptoms.

5. Conclusion

We found that CD is more prevalent among patients referring with typical symptoms of malabsorption specially chronic diarrhea than patients with atypical symptoms. Any patient who has classic symptoms of CD should undergo duodenal biopsy, irrespective of whether serologic testing for CD has been performed or was positive. In patients with atypical symptoms, serological tests should be performed followed by endoscopic biopsy. In these patients, routine duodenal biopsy is recommended when endoscopic evaluation is indicated.

Conflict of Interests

The authors did not declare any conflict of interests.

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