Chapter 10

Extraintestinal Manifestations of Celiac Disease and Associated Disorders

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Abstract

Celiac disease is not limited to the gastrointestinal tract and belongs to the group of autoimmune systemic diseases. It is frequently accompanied by a variety of extra digestive manifestations. More than half of the patients with adult celiac disease present with extra intestinal manifestations. The majority improve on a gluten-free diet. It is therefore advisable to have a low threshold of suspicion for the diagnosis.

The most frequent extraintestinal manifestations are iron deficiency anemia, osteoporosis, and dermatitis herpetiformis. The causes for the onset and manifestation of associated diseases are diverse; some share a similar genetic base, like type-1 diabetes mellitus; others share pathogenic mechanisms, and yet, others are of unknown nature. The implementation of a gluten-free diet improves the overall clinical course and influences the evolution of the associated diseases. In some cases, such as iron deficiency anemia, the gluten-free diet cures the manifestations and in other disorders, like in type-1 diabetes allows a better control of the disease. In several associated diseases, an adequate adherence to a gluten-free diet may slow their evolution, especially if implemented at an early stage.

We have reviewed in this chapter, first, the intra and extra intestinal manifestations of celiac disease, such as oral manifestations, hematological disorders, and osteoporosis. Secondly, the gluten-related associated diseases with genetic links, such as dermatitis herpetiformis and gluten ataxia. Finally, from the associated diseases we have reviewed type-1 diabetes mellitus, thyroid diseases, and malignancy.

Keywords

Celiac disease, extraintestinal manifestations, associated disorders, gluten-related diseases, anemia, osteoporosis, malignancy.

1. Introduction

Celiac disease is a process of autoimmune nature, induced by the ingestion of gluten genetically predisposed individuals[1]. It usually affects the digestive tract, which is classically associated with the presence of diarrhea, malabsorption, and weight-loss. In the last few decades the protean clinical presentation accompanied by a series of extraintestinal manifestations has substituted the classical presentation. The most frequent extraintestinal manifestations are iron deficiency anemia, osteoporosis, and dermatitis herpetiformis[2].

Recent studies have confirmed that autoimmune diseases are between 3 to 10 times more frequent in patients with celiac disease than in the general population[3,4].

The most prevalent are type-1 diabetes mellitus[5-7], autoimmune thyroid disease[8,9], Sjögren's syndrome[10], Addison's disease[11], autoimmune hepatitis[12-14], autoimmune cholestatic liver disease[15] and primary biliary cirrhosis[16-18]. Some reports of patients rheumatoid arthritis with celiac disease and other reports with dermatitis herpetiformis have been published. However, there is no evidence of a systematic association. Interestingly, from the genetic point of view, sharing of several genes within these diseases[19,20] are significantly increased. A study on the causes of mortality has identified an important number of patients who died of celiac disease, also had rheumatoid arthritis[21]. These observations suggest that the study of the association between rheumatoid arthritis and gluten related disorders should be systematically approached.

Several hypotheses have been put forward to explain the increased prevalence of autoimmune disease in patients with celiac disease. One of the hypotheses posits that a longer duration in the exposure to gluten before diagnosis, could be a risk factor for the development and emergence of related diseases[22,23]. However, other authors found that the prevalence of autoimmune diseases in patients with a late celiac disease diagnosis does not correlate with the duration of gluten intake[4].

Also the presence of the HLA-DQ2 and HLA-DQ8 in common with type-1 diabetes mellitus, autoimmune thyroid and Addison's disease shows a genetic link. It still remains to define which are the immunological mechanisms involved in the emergence and development of other autoimmune diseases in patients with celiac disease. The association of celiac disease with the HLA antigens may help to understand the mechanisms that link food-proteins intolerance to autoimmunity. It even has been suggested that celiac disease is a model for understanding autoimmune disease[24-27]. Like all autoimmune disorders celiac disease has a multifactorial etiology as well as the genetics of a complex disease[28].

From the immunological point of view, in celiac disease there is an overexpression of interleukin (IL)-15 in the mucosa of the small intestine. There is some evidence that due to the presence of this cytokine, effector T cells in the intestinal epithelium are not suppressed by regulatory T cells causing loss of tolerance to gluten and antibodies to self-antigens[29].

Another factor that has been implicated in the pathogenesis of autoimmunity in celiac disease is deficiency of vitamin D as this deficiency is commonly found in patients suffering from celiac disease and in other autoimmune disorders. Vitamin D was used to treat osteoporosis. Presently it has become an important biological inhibitor of inflammatory hyperactivity even in the presence of several malignant tumors. Its role is not yet fully understood[30].

In this chapter the following medical disorders will be reviewed:

First, the intra and extraintestinal manifestations of celiac disease, such as oral manifestations, hematological disorders, and osteoporosis.

Second, gluten-related associated diseases with genetic links, such as dermatitis herpetiformis and gluten ataxia.

Third, associated diseases such as Type-1 diabetes mellitus, Thyroid diseases, and malignancy.

In the available medical literature casual associations to other diseases have been found although no proper systematic studies have been published and will not be described.

Non-celiac gluten sensitivity and gluten allergy are comprehensibly described in other chapters of this book.

2. Oral and Dental Manifestations of Celiac Disease

The mouth and teeth are now widely recognized as tissues characteristically affected by celiac disease. In fact, several oral disorders have been related with celiac disease, including delayed eruption of teeth, enamel defects, recurrent aphthous oral ulcers, oral lichen planus, cheilosis, atrophic glossitis, glosodinia, and Sjögren syndrome. A celiac disease-characteristic pattern of T-cell inflammation has been also described in the oral mucosa of celiac patients[31,32].

2.1. The Oral Mucosa of Celiac Patients

Several studies have assessed the presence of histopathological changes in the oral mucosa of celiac patients[33,34], where a dense infiltration by T-lymphocytes, similar to that documented in the small bowel mucosa, has been repeatedly demonstrated; furthermore, a gluten-free diet was able to modify the T-cell populations[35]. Beyond the challenging potential of the oral mucosa as an easily accessible tissue to simplify the diagnosis of celiac disease[36], the involvement of the oral cavity and the capacity to produce anti-endomisial and anti-transglutaminase antibodies[37], allows the screening of celiac disease through salivary samples[38].

2.2. Aphthous Stomatitis

The association between recurrent aphthous ulcerations and celiac disease was described 4 decades ago, after documenting an unexpectedly high proportion of atrophic jejunal mucosa in patients with troublesome recurrent aphthous ulceration[37]. All patients remitted completely on a gluten-free diet, and the aphthous ulceration did not recur. Gluten withdrawal also showed a favorable response in many patients without villous atrophy[39]. Further

research has strengthened the link between oral aphthae and symptomatic as well as subclinical celiac disease[40,41]. The presence of recurrent aphthae is now recognized as one of the most frequent atypical associated conditions[42] which affects up to 20% - 40% of celiac patients at some stage in life. A significant association between oral aphthous ulcers and enamel defects in celiac patients has been described in some but not in all studies[43].

Aphthous oral ulcers have been recognized as risk factor for celiac disease. This justifies the screening of celiac disease in cases of recurrent or troublesome aphthous ulcers. A serological screening test is recommended as the initial method. Small intestinal biopsies should also be considered even if serology is negative. Favorable responses to a gluten-free diet have been documented in patients who showed an increase in intra-epithelial lymphocytes within the small bowel epithelium (stages Marsh 1/Coraza A)[44]. The improvement of oral aphthous stomatitis after a gluten-free diet has been demonstrated[45].

2.3. Delayed Dental Age in Celiac Children

Celiac disease in childhood may deprive of several nutritional factors, which are essential not only to promote body development, but also dental eruption. In fact, teeth development appears delayed or is slowed down in celiac children compared to healthy subjects[46]. Celiac disease has been also reported to influence the mineralization of permanent teeth[47].

2.4. Enamel Defects

Dental enamel defects are the imperfections in the enamel, which is the hard mineralized surface of teeth that makes up the normally visible part of the tooth, covering the crown. The tooth enamel is the hardest substance in the human body and contains the highest percentage of minerals, 96%, with water and organic material composing the rest. Dental enamel defects, mainly characterized by pitting, grooving and sometimes by complete loss of enamel, were firstly reported in children with celiac disease by Aine in 1986[48]. Since

this publication, repeated reports have led to *The North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition* to include the presence of specific dental enamel defects as a risk factor for celiac disease[49].

Enamel defects include both discoloration and structural changes, as shown in Table 1.

Table 1. Classification of Systemic and Chronologic Enamel Defects. Modified from Aine in 1986[48].

Classification	Enamel Defect
Grade 0	No defect
Grade I	Defect in color of enamel consisting of single or multiple cream, yellow or brown opacities (marks) and loss of normal enamel glaze.
Grade II	Slight structural defects consisting of a rough surface with horizontal grooves or shallow pits; light opacities and color changes may also be found. Part of or the entire surface of enamel is without glaze.
Grade III	Obvious structural defects with partly or entire surface of the enamel is rough and filled with deep horizontal grooves. This may vary in width or have large vertical pits; large opacities of different colors or linear discoloration may be present in combination.
Grade IV	Severe structural defects. Shape of the tooth is changed. The tips are sharp-pointed and/or the incisal edges are unevenly thinned and rough. The thinning of the enamel material is easily detectable and the lesion may be strongly discolored.

The exact mechanism leading to these defects remains unclear; immune-mediated damage has been involved as the primary origin[50]. Also nutritional disturbances, especially hypocalcemia, seem to play an important role[51]. A gluten-induced stimulation of naïve lymphocytes in the oral cavity has also been hypothesized[31]. Ultrastructural analyses have demonstrated that the enamel hypoplasia of deciduous and permanent teeth in celiac disease patients is highly hypomineralized with shorter prisms of hydroxyapatite,

more irregularly distributed and less interprismatic substance than observed in the non-celiac enamel hypoplasia[52].

A significant increased prevalence of enamel defects has been repeatedly reported in children, adolescents and adult subjects with celiac disease[43,53], and also in patients with dermatitis herpetiformis. There is no correlation between the degree of enamel defects and that of the mucosal damage in small bowel biopsy specimens[53].

Finally, dental enamel defects are not specific for celiac disease, having been also associated with an excessive fluoride intake, tetracycline exposition or bulimia[43]. In these conditions, dental enamel defects are not as severe as those identified in celiac patients[54,55].

2.5. Caries Risk and Celiac Disease

Dental caries remains today as one the most common diseases throughout the world, affecting 1/3 of the population of their permanent teeth[56]. It consists in a bacterial infection with production of acids, which in case of excess of remineralization factors, leads to demineralization and destruction of the hard tissues of the teeth, including the enamel, dentine and cementum.

In spite of having been recognized as the most common childhood disease, a significantly increased prevalence of caries has been reported in subjects with celiac disease compared to matched controls in several observational studies[32]. The proportion of caries-free subjects in the control group was found to be 2-fold higher than in the celiac disease group before starting on a gluten-free diet[57].

2.6. Oral Lichen planus

Lichen planus is a disease of the skin or mucous membranes that resembles vegetal lichen. It presents with a variety of lesions, the most common is a well-defined area of purple-colored, itchy, flat-topped papules with interspersed lacy white lines[58]. This is possibly the result of an autoimmune process with an unknown initial trigger. Lichen planus in the mouth may

persist for many years, and is difficult to treat, with relapses being common[59]. Atrophic/erosive lichen planus is associated with a small risk of malignant transformation. There is no cure for lichen planus, so treatment is for symptomatic relief or due to cosmetic concerns.

From the first description of the association of celiac disease and oral lichen planus in 1993[60], an increased prevalence of celiac disease in patients with oral lichen planus has been repeatedly reported, generally using serological screening[61]. These authors conclude that celiac disease screening should be considered in oral lichen planus patients, since untreated celiac disease can present many complications and reduce a patient's quality of life.

2.7. Atrophic Glossitis and Other Tongue-related Symptoms

Atrophic glossitis is an inflammatory condition of the tongue mucosa that is characterized by a smooth, glossy appearance with a red or pink background. This is due to the atrophy of filiform papillae that causes the development of circinate erythematous ulcer-like lesions of the dorsum and the lateral border of the tongue[62]. Several diseases have been primarily related with atrophic glossitis, including chemical irritations, local and systemic infections such as candidiasis, amyloidosis, drug reactions, nutritional deficiencies, pernicious anemia, malnutrition, sarcoidosis, Sjögren's syndrome, psoriasis[63], and celiac disease[64]. The tongue was the most frequently affected site in a series of 128 patients with celiac disease who were examined for oral mucosal lesions and symptoms, with 29.6% of the patients describing soreness or a burning sensation and 8.6% having erythema or atrophy[33]. This recognition should lead dentists to play a more significant role in screening for celiac disease, to widen the possibility of a correct diagnosis and subsequent treatment.

2.8. Sjögren's Syndrome

This chronic autoimmune disease is characterized by a destruction of exocrine glands, specifically salivary and lacrimal glands, caused by

lymphocytic infiltration[65]. The association of celiac disease with primary Sjögren's syndrome, as with other immune-mediated disorders, has been described in the literature. In Hungary it was found in 111 patients with Sjögren syndrome that celiac disease was significantly higher than in the non-Sjögren syndrome European population (4.5: 100 *vs.* 4.5-5.5: 1,000)[66]. Even when following a gluten-free diet does not usually result in the resolution as both disorder evolved independently, the evaluation of celiac disease in patients with must be considered[67].

3. Hematological Manifestations of Celiac Disease

Within the hematological manifestations of celiac disease, anemia remains the most common due to iron, folate, and occasionally vitamin B12 deficiency. Anemia may be the sole presenting symptom. Other manifestations include thrombocytosis, leukopenia, thromboembolism, increased bleeding tendency, immunoglobulin (Ig)A deficiency, spleen dysfunction, and lymphoma[68]. In a recent nationwide prospective population-based cohort study in Sweden has been found that individuals with IgA deficiency more often had celiac disease (6.7 % *vs.* 0.19 % in controls) and type-1 diabetes (5.9 % *vs.* 0.57 %) corresponding to a 35-fold higher prevalence ratios for celiac disease and 10-fold higher for type-1 diabetes. These individuals with IgA deficiency have a higher prevalence of several other autoimmune disorders[69]. These findings should be taken into account in screening programs to detect celiac disease.

3.1. Anemia and Celiac Disease

Anemia without other clinical clues of intestinal malabsorption is one of the most common extraintestinal manifestations of celiac disease[70,71]. Although folate and vitamin B12 deficiency are known complications of celiac disease, the most common nutritional type of anemia associated with celiac disease is iron deficiency.

Celiac disease is frequently diagnosed in patients referred for evaluation of iron deficiency anemia, being reported in 1.8%-14.6% of patients[72].

In one large study in Italy of 42 centers with patients presenting subclinical celiac disease, iron-deficiency anemia appeared to be the most frequent extraintestinal symptom in children and in adults[71]. A characteristic feature of the iron deficiency anemia associated with celiac disease is its refractoriness to oral iron treatment[73].

Since anemia is a common presenting feature of celiac disease, what is the chance of finding celiac disease in patients presenting with iron deficiency anemia? This question is of particular importance for hematologists and general practitioners who are often consulted for unexplained iron deficiency anemia. Table 2 shows that celiac disease in this group of patients occurs between 4.8 and 6%. Most of the studies included a majority of premenopausal females. The most consistent clinical feature in the series of Table 2 was the complete refractoriness to oral iron treatment and the complete absence of a rise in serum iron two hours after an oral iron doses of 100 mg ferrous sulphate tablets[74-79].

Table 2. Prevalence of celiac disease in patients with chronic iron deficiency anemia.

Year and Ref	n	Serology	Biopsy	Celiac Disease (%)
1995[74]	200	+	+	5.0
1998[75]	85	–	+	5.8
2001[76]	71	–	+	5.6
2002[77]	258	+	+	4.8
2005[78]	150	+	+	5.3
2008[79]	116	+	+	6.0

n = number of included patients; (–) means not performed. Modified from Hershko and Patz[80].

A prospective study of patients with iron deficiency anemia published in 2005[78] found a prevalence of celiac disease of 5%. Subsequent studies have confirmed that about 4% to 6% of patients with obscure refractory iron deficiency anemia have celiac disease. Autoimmune gastritis is encountered in 20% to 27% of patients, 50% of these have active *H. pylori* infection and are permanently cured by eradication[81].

The most obvious cause of anemia is an impaired absorption of iron and other nutrients including folate and cobalamin. Villous atrophy of the intestinal mucosa is an important cause of abnormal iron absorption which is reflected in the laboratory evidence of iron deficiency anemia in most anemic patients with celiac disease[79].

Abnormal iron absorption is also supported by the failure to increase serum iron following an oral iron supplement and refractoriness to oral iron treatment. Other factors may contribute to cause anemia, which in many cases is multifactorial in etiology[82].

Occult gastrointestinal blood loss as a cause of anemia in celiac disease is doubtful, since the evidence supporting an increased fecal blood loss in celiac disease is controversial. Although abnormal intestinal bleeding may occur in some celiac patients, it does not appear to play a significant role in the cause of anemia[83].

Bergamaschi et al., focused on the role of anemia of chronic disease in the differential diagnosis in series of 150 anemic patients with celiac disease at presentation. The authors found 45 patients who had uncomplicated iron deficiency anemia and 2 had vitamin B12 or folate deficiency. The iron status parameters which identified anemia of chronic disease alone or anemia in combination with iron deficiency (6 patients) showed a prevalence of 17% concluding that the anemia of chronic disease plays a significant role in celiac disease. A gluten-free diet resolved the different mechanisms leading to anemia in these patients[84].

From a practical point of view, in absence of markers of chronic disease, such as increased C-reactive protein, elevated sedimentation rate or high fibrinogen levels, presence of underlying inflammatory gastrointestinal disease,

celiac disease, chronic autoimmune and/or *H. pylori* gastritis cannot be excluded. The sensitive and accurate indicators employed by Bergamaschi et al.[84] such as the measure of the ferritin/transferrin ratio, serum levels of interferon gamma (IFN-γ) and other markers of inflammation may facilitate the differential diagnosis and the identification of an underlying inflammatory condition that may explain the cause of the anemia and guide to an effective treatment.

4. Bone Metabolism and Bone Mineral Density in Celiac Disease

The association of celiac disease with metabolic bone disorders has been known even before the origin and treatment of celiac disease; Osteomalacia, a disease characterized by low bone mineral density (BMD), marked deformities and rickets, has been repeatedly described among children with celiac disease in the early literature[85]. Rarely it is part of the initial presentation of celiac disease in children[86]. The development and availability of the bone density scan as a non-invasive diagnostic technique has confirmed the link between low BMD and celiac disease. For adult patients the BMD-scan is used since 2005[87]. Today, metabolic bone disease remains a significant and common complication of celiac disease found at the time of diagnosis in both children and adults. Low BMD leads to an impaired deterioration in quality of life[88], aggravated by its clinical manifestation such as fractures.

At present, a low BMD constitutes the first diagnostic criterion for osteoporosis, a skeletal metabolic disease further defined by impaired bone microarchitecture, increased bone fragility and susceptibility to bone fractures. The WHO establishes a diagnosis of osteoporosis when bone mass values are below -2.5 standard deviation (SD) of peak bone mass (i.e. the maximum BMD value reached by an adult), and osteopenia when those values are located between -1 SD and -2.5 SD (Table 3).

Table 3. The World Health Organization (WHO) diagnostic criteria for post-menopausal Caucasian women.

Diagnosis	BMD criteria (T-score)
Normal	BMD T > –1 SD
Osteopenia or low bone density	BMD T < –1 SD and > –2.5 SD
Osteoporosis	BMD T < –2.5 SD
Severe osteoporosis	BMD T< –2.5 SD + fracture

T-score: comparison with BMD value in average reference population. SD: Standard deviation. BMD: Bone mineral density.

Severe or established osteoporosis associates with a current or past fragility fracture. A low BMD defining osteoporosis in children and adolescents consists in an area of BMD of less than 2 standard deviations (SD) below the age-adjusted mean value (Z-score < -2 SD)[89]. Osteoporosis is similar to celiac disease in terms of missed diagnosis and therefore a lower prevalence than expected is found. It has been hypothesized that celiac disease could explain part of the considerable idiopathic osteoporosis "mixed bag"[90]. Nonetheless, despite many studies on this subject, a description of how celiac disease –a primarily digestive disorder– can affect bone metabolism has yet to be fully elucidated.

4.1. Prevalence of Osteoporosis Among Patients With Celiac Disease

It is estimated that at the moment of diagnosis, one-third of pediatric patients have osteoporosis, one-third osteopenia and only the remaining one-third of patients with celiac disease has a normal BMD[91]. Despite the fact that more than half of the children with celiac disease present with low BMD at the moment of diagnosis[92], once the gluten-free diet is instituted, most celiac children catch up to their height-weight growth curve and accelerate their rate of bone mineralization, so that most achieve normal peak bone mass by the time bone growth is completed[93]. The main problem arises when celiac

disease is diagnosed during adulthood, once bone growth is complete and peak bone mass has been reached[94]. The prevalence of osteoporosis in adult patients with celiac disease is twice that of the non-affected population in the same age group[95]. The average prevalence of low BMD among adult celiac patients compared to the general population is around 40%. In some series of patients with celiac disease this prevalence reached up to 75%[96]. This low BMD also affects patients with dermatitis herpetiformis[97].

A low BMD has been demonstrated in celiac patients with classic symptoms[98], in patients with sub-clinical manifestions[99], and even in asymptomatic patients with celiac disease[100,101]. Therefore, the type of celiac disease-related symptoms cannot predict the presence of low BMD, and justifies attempts to reach the low BMD diagnosis by further searching for other determinants.

Since osteoporosis is a common complication of celiac disease, it is appropriate to consider whether or not to screen for celiac disease in patients with idiopathic osteoporosis. Although there is no definitive consensus, the greater weight of opinion is in favor of the screening strategy since the frequency of celiac disease is 10 times higher than expected in patients with osteoporosis[102]. A similar frequency of celiac disease among type-1 diabetic mellitus already justifies universal screening among these patients (see later). In fact, celiac disease screening through specific antibodies in patients with osteoporosis has led to an increase in the diagnosis of celiac disease between 4[103] and 17[102] times higher prevalence.

4.2. Etiology and Pathogenesis of Low BMD in Celiac Disease

The origin of osteoporosis in celiac disease has been classically associated with malabsorption caused by intestinal villous atrophy and poor absorption of calcium and vitamin D[104], as well as secondary hyperparathyroidism, even in patients with normal vitamin D serum levels[105]. Low consumption of dairy products[106], failure to ever reach peak theoretical bone mass[107], higher degree of duodenal injury in biopsy specimens[108], and greater delay in the diagnosis

of celiac disease[109] have also been directly related to the pathogenesis of low BMD in celiac patients.

Vitamin D deficiency is common among patients with celiac disease, although there are no changes in the expression of vitamin D receptors[110] nor a greater number of receptor gene mutations interfering with the metabolism of this vitamin in the celiac population[111]. Restricted milk intake may exacerbate vitamin D deficiency; in fact, co-occurrence of lactose intolerance is common among celiac patients and is estimated at 10%, but may increase to 50% in the presence of obvious symptoms of malabsorption[112]. However, one must bear in mind that diet only provides 5-10% of the required vitamin D, the rest being obtained from exposure to sunlight. Even so, studies of celiac patients have failed to establish a clear association between vitamin D levels and bone impairment, as demonstrated for inflammatory bowel disease[113].

Deficits in other fat-soluble vitamins (A, K and E) and water-soluble vitamins (C, B12, folic acid and B6) or minerals (such as iron, calcium, phosphorus, copper, zinc, boron, fluorine), which are required for normal bone metabolism[112,114], may be the result from the intestinal malabsorption and contribute to impaired BMD.

Celiac patients on a gluten-free diet frequently exhibit high serum parathyroid hormone (PTH) levels[114]. Secondary hyperparathyroidism may explain the higher prevalence of bone loss in the appendicular skeleton compared with the axial skeleton in celiac disease[115].

Reduced serum levels of insulin-like growth factor-1 (IGF-1) also called somatomedin C[116], constitute an additional hormonal factor which has been involved in patients with a lower bone mass. This reduced level was associated with decreased serum levels of zinc[117], which normalized after introduction of a gluten-free diet.

Chronic inflammation determines changes in bone metabolism via several pro-inflammatory cytokines, such as tumor necrosis factor alpha (TNF-α), IL-1beta, IL-6 or gamma interferon. TNF-related cytokines include the receptor activator of nuclear factor kappa-B (RANK), its ligand (RANKL), and osteoprotegerin (OPG). RANKL is secreted by activated T lymphocytes

and is a key molecule in the regulation of bone metabolism. RANKL has proved to be a survival factor whose primary function is activation of osteoclasts, the cells involved in bone resorption[118].

Serum levels of RANKL and OPG are high in patients with celiac disease[119], The OPG/RANKL ratio is directly associated with IL-6 serum levels and lumbar bone mass[120]. Thus, adult women with celiac disease have OPG/RANKL ratios significantly lower than controls, despite adherence to a gluten-free diet; this correlates with a lower lumbar BMD[121].

Finally, the etiology of osteoporosis in celiac disease coincides with the factors shared with the rest of the population such as family history, age, menopause, physical activity, smoking, as well as other specific factors such as genetic influence, the above-mentioned vitamin deficiencies, hormonal changes and the inflammatory process itself.

The years of exposure to gluten in the diet before the diagnosis of celiac disease do not appear to influence BMD significantly nor does early menopause. There is little data on the influence of patient gender on BMD, but most studies show no difference in this respect. Another factor associated with poor bone condition is a low body mass index (BMI). Patients with persistent villous atrophy despite proper adherence to the gluten-free diet (refractory celiac disease) are particularly susceptible to osteoporosis, with a prevalence of 58% compared to the 22% reported among gluten-free diet responsive patients[122].

4.3. Diagnosis of Low Bone Mineral Density in Celiac Disease

All patients in whom there is clinical suspicion of osteoporosis should undergo a thorough history-taking and physical examination so as to identify other risk factors and/or consequences. In the case of celiac disease, it has been suggested that all patients diagnosed in adulthood should undergo bone density scans[123], since conventional radiography has not proven to be a specific or sensitive method in assessing changes in bone mass. However, some studies, seeing the low risk of bone fracture among celiac patients, have questioned the utility of routine bone density scans[124]. Recent studies advocate densitometric

assessment in all celiac patients diagnosed during adulthood who have villous atrophy on duodenal biopsies and/or laboratory values suggestive of malnutrition or malabsorption, regardless of their symptoms[108]. The greatest benefit from bone density scans is determining whether there is osteoporosis and the degree of impairment, so that a treatment regimen can be planned. However, the optimal timing to perform bone density scans in celiac patients, whether at the time of celiac disease diagnosis or after a period of adherence to the gluten-free diet, has motivated some controversy. Celiac children show a great bone recovery capacity after starting a gluten-free diet, so no further studies seem to be necessary until their growth period is completed.

4.4. Bone Fracture Risk in Celiac Disease

Due to the increased prevalence of osteoporosis, celiac patients have a high risk of bone fractures compared with the unaffected population of the same age and gender. Up to one in four adult patients may have an established history of fractures[125,126], which produces a significant deterioration in quality of life.

As in other aspects of the relationship between celiac disease and osteoporosis, quantification of fracture risks in different studies shows mixed results. These discrepancies are largely due to differences in data collection, mainly from fracture reports, questionnaires, or hospital admissions. It is therefore possible that the prevalence of fractures (vertebral, hip, and overall) is underestimated in the celiac population. One of the common issues of fracture risk studies is that they lack proper morphometric assessment of the spine, which underestimates fractures at that level[127], or failure to use validated questionnaires or methods, such as the FRAX® (Fracture Risk Assessment Tool) index proposed by the WHO[128-130]. Several studies have estimated the incidence and prevalence of bone fractures among patients with celiac disease[131] (Table 4). The results have been summarized in two systematic reviews: The first one included 20,955 celiac disease patients, 1,819 (8.7%) had fractures and 96,777 controls with 5,955 (6.1%) fractures, which resulted in a pooled odds ratio of 1.43 (95% confidence interval (CI), 1.15 to 1.78), with a significant heterogeneity among the studies[132]. The baseline was associated with a 30%

increase (95%CI, 14% to 50%) in the risk of any fracture, and a 69% increase in the risk of hip fracture 136 (95% CI, 10% to 259%).

Table 4. Studies of fracture risk available in adult patients with celiac disease. Adapted from Scott, 2000[142].

Year Country	Subjects CD-Controls (C)	Design of study	Diagnostic methods	Fractures	Risk of fracture OR(95%CI)
2000 Argentina[127]	165 CD – 165 C Matched controls with GI symptoms	Cross-sectional Retrospective Analysis	Dual energy x-ray Densitometry Spine radiography	Peripheral Lumbar spine	3.5 (1.8 - 7.2) 2.8 (0.7-11.5)
2001 UK[133]	75 CD – 75 C Control matched by Age and sex	Cross-sectional Retrospective Analysis	Dual energy x-ray Absorptiometry of Lumbar spine and Femoral neck	Any location	21% in CD versus 3% in C
2002 Denmark[134]	1,021 CD – 3,063 C Control matched by Age and sex	Computerized Registered of national hospitals admissions & discharges	Diagnoses of fractures in cases and controls in the same national registry	Any Lumbar Distal radius (Colles) Neck of femur	RRI 0.7 (0.45-1.09) RRI 2.14 (0.70-6.57) RRI 2.00 (0.58-6.91) RRI 0.71 (0.27-1.89)
2003 UK [135]	244 CD – 161 C Controls paired for age and sex	Analysis of celiac population records	Lifestyle and general health questionnaire, with specific questions about history of fractures	Any location Forearm	1.05 (0.68-1.62) 1.21 (0.66-2.25)
2003 UK[126]	4,732 CD – 23,620 C 1,589 CD "incidents" controls matched by age and sex	Population cohort study from a database	Codified registry of fractures in patients with CD and controls	Any location Hip Ulna, radius	HR 1.30 (1.16-1.46) HR 1.90 (1.20-3.02) HR 1.77 (1.35-2.34)
2004 Argentina[136]	148 CD – 292 C Matched controls with GI symptoms	Cross-sectional study of cases and controls	History of fracture based on interview with a predefined questionnaire	any	5.2 (2.8 - 9.8) in "classic" CD 1.7 (0.7 - 4.4) in "asymptomatic" CD
2005 UK[137]	383* – 445 C *celiac women over 50 years of age	Cross-sectional study	Detailed questionnaire about history of fractures	Any location	1.51 (1.13-1.5)

Year Country	Subjects CD-Controls (C)	Design of study	Diagnostic methods	Fractures	Risk of fracture OR(95%CI)
2007 Sweden[138]	13,000 CD – 6,500 C 4,819 adults CD controls matched by age and sex	Cross-sectional population cohort study based on hospital discharge records	Records of 1st documented fracture at any location	Any location Hip	HR 1.4 (1.3-1.5) HR 2.1 (1.8-2.4)
2008 USA[139]	83 CD – 166 C	Retrospective cohort, retrospective case-control	Clinical history and the radiologist's report of each fracture	All fractures. Fractures of the hip, spine, or distal forearm that result from minimal or moderate trauma in patients <35 years were considered osteoporotic fractures	2.0 (1.0–3.9)
2011 Argentina[140]	265 CD – 530 C	Retrospective cohort	Standard questionnaire on CD and fracture history through in-person interviews	All fractures	HR=1.78 (1.23–2.56) (before diagnosis of CD)
2011 Finland[141]	35 CD screen-detected CD patients	Case series study	Dual energy x-ray absorptiometry of lumbar spine and femoral neck	All fractures	Low-energy fractures in 8/35 of CD patients; 22.8 %
2012 Spain[108]	40 CD patients with a diagnosis of CD in adulthood	Prospective cross-sectional	Dual energy x-ray densitometry, FRAX® tool	Risk of hip fracture Risk of major osteoporotic fracture (lumbar, femoral neck, forearm and shoulder)	3.5 times greater in Marsh 3 on 1-2 1.34 times greater in Marsh 3 on 1-2

CD, coeliac disease; OR, odds ratio; RRI, relative risk increase; HR: hazard ratio; (95%CI), 95% confidence interval.

The risk of fracture at 10 years estimated at the time of celiac disease diagnosis was determined by using the FRAX® tool in a recent Spanish

research study[108]. A moderate risk of fracture was demonstrated among patients with duodenal villous atrophy (Marsh stage 3), which was 3.5 times higher than in patients without villous atrophy (Marsh stage 1 or 2). More recently, a Swedish cohort study, has found that persistent villous atrophy on follow-up biopsy is predictive for hip fracture risk but not overall fractures, irrespective of patients' age[143]. The authors stated that persistent villous atrophy could result in a decreased body mass index and a reduction on its protective role against fall and trauma.

4.5. Treatment of Low Bone Mineral Density in Patients with Celiac Disease

The first-line treatment for osteoporosis in celiac disease is gluten-free diet. Many studies have demonstrated its effect on bone density and calcium absorption in both children and adults[144-146]. The greatest bone mass gain described in these studies is during the first year of instituting a gluten-free diet. It leads to a 5% increase in bone mass after 1 year[144], although this is not enough for bone mass to normalize. In clinical practice, the degree of adherence to the gluten-free diet also determines the recovery of bone mass, which is generally estimated to be around 30%[147-149]. Furthermore, the recovery rate is higher in young celiac patients[150] than among adults[144]. This is largely explained by the fact that 97% of bone mass is gained in the first two decades of life and full recovery is difficult after this time.

BMD loss associated with pediatric celiac disease responds to gluten-free diet continuously and gradually, with almost complete restoration of bone mass after about two years' treatment[151]. The earlier the age at which the gluten-free diet is started, the better and faster is the response[152]. In fact, it is estimated that an increase in BMD will only take place if the gluten-free diet is started before the age of 25[104]. The strict adherence to a gluten-free diet is so important for bone metabolism that lack of improvement in BMD after its introduction has been associated with persistent duodenal lesions[153].

In addition to the gluten-free diet, an adequate daily intake of calcium and vitamin D should be ensured, as it is a critical factor for bone mass

acquisition and maintenance. Untreated adult celiac patients have shown a 45% reduction in calcium absorption followed by an improvement of 52% after 6 months of gluten-free diet adherence[104]. Regarding vitamin D, at the time of diagnosis, less than 5% of Spanish adult celiac disease patients had normal serum levels[108]. A daily intake of 1,200-1,500 mg calcium and 400U vitamin D3 is recommended and as in all other forms of osteoporosis. Adherence to drug therapy, as to the gluten-free diet, is a crucial aspect of treatment, so patients must be kept motivated. In fact, these patients will most commonly abandon treatment with calcium and vitamin D, as it must be taken daily, while hormonal therapy and bisphosphonates (which are administered weekly) are usually adhered to correctly. Drug treatment would be indicated for patients who do not achieve bone mass recovery goals, and would not differ from that established for other causes of osteoporosis.

In these cases bisphosphonates are the recommended first-line therapy. However, as far as we know there is no data on the effect of bisphosphonates in celiac disease-associated osteoporosis.

5. Gluten-Related Disorders

5.1. Dermatitis Herpetiformis

Dermatitis herpetiformis was firstly described in 1884 by the French dermatologist Louis Duhring[154]. In some countries, this disease is still called Duhring's disease. In 1966, Marks et al. identified the presence of histological abnormalities in the small bowel, identical to those observed in patients with celiac disease[155]. The patients have gluten-induced IgA autoantibodies against tissue transglutaminase (tTG)-2 and tTG-3[156]. Dermatitis herpetiformis is regarded as the skin manifestation of gluten sensitivity[157,158]. The autoimmune basis is confirmed by the characteristic findings of the presence of IgA deposits and tTG at the dermo-epidermal junctional level. Its etiology is multifactorial and has a polygenetic basis. Dermatitis herpetiformis is like celiac disease associated with a number of autoimmune diseases such as IgA

deficiency, type-1 diabetes mellitus, autoimmune hypothyroidism and Addison's disease[159-161].

Primary cutaneous lesions appear as erythematous papules associated with vesicles filled with liquid, in patches distributed symmetrically on extensor surfaces[162]. As the vesicles are very itchy, patients scratch themselves rupturing the blisters, releasing its liquid content and give rise to erosions and abrasions. Subsequently, papules become scabs and fall off leaving a slightly pigmented area. It usually predominates in young adults but children and the elderly may be affected, especially in atopic children. The vast majority of patients report the onset of symptoms in hot months, from early spring to late summer. [163,164].

Usually the eruptions are symmetrical, affecting mainly the surface extension of the upper and lower limbs, predominantly in elbows and knees but also ankles, waist, neck and buttocks. The face, scalp and groins can be affected. The localization of lesions on the palms of the hands but not on the back is also relatively frequent. They also may appear on the fingers, these lesions appear in the form of petechial pads. The aspect of the lesions adopts a very similar appearance in the great majority of affected patients, which facilitates its early diagnosis[165]. Mucosal involvement is rare. The diagnosis of dermatitis herpetiformis is established clinically, histologically and immunopathologically.

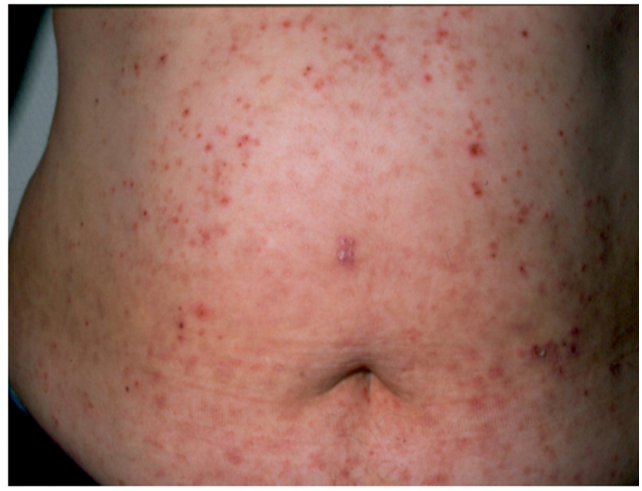

Figure 1. Many characteristic lesions in different stages of evolution in the abdomen in a patient with dermatitis herpetiformis, an unusual localization.

The majority of patients with dermatitis herpetiformis does not have, or present few intestinal manifestations. Sometimes the patients only have iron deficiency anemia. Males are affected more than females (1.5-2 to 1) as opposed to celiac disease, which shows a clear predominance in females (2-4 to 1)[166].

The most characteristic histological finding is the confirmation of the presence of granular IgA deposits localized at the level of the papillae of the dermis and along the basement membrane, demonstrable by direct immunofluorescence in skin biopsies. These accumulations promote an inflammatory response with infiltration of neutrophils and vesicles in the affected areas[167]. The immunological basis for its development is closely linked to the pathogenesis of gluten intolerance in celiac disease. tTG-3 antibody is the main auto-antigen and it is located on the skin of these patients, triggering an inflammatory response[168].

The association with genetic markers from HLA class-II, mainly HLA-DQ2 and/or HLA-DQ8, is the same as seen in celiac disease. A genome-wide association study (GWAS) in celiac disease in North America has provided suggestive statistical evidence for the association of dermatitis herpetiformis and microscopic colitis with SNPs at chromosomes 3p21.31, 6q15, 6q25, 1q24.3 and 10p11.23[169].

The main treatment of dermatitis herpetiformis is a gluten-free diet, which should be strictly maintained during lifetime. The skin lesions disappear within various weeks after initiating a gluten-free diet. Some cases may require a short complementary treatment with dapsone. This drugs target the skin eruption inhibiting neutrophil migration and is used temporarily, until the complete disappearance of the skin lesions[170]. A survey in Finland from 1971 to 2010 on the mortality rate and causes of death in 476 consecutive patients with dermatitis herpetiformis documented significantly reduced all-cause and cerebrovascular disease mortality. The standardized mortality rate for all causes of death was significantly reduced, being 0.70 (95% CI, 0.55 to 0.87), similar in both sexes and was equal in patients with dermatitis herpetiformis with (0.73) and without (0.77) small bowel villous atrophy[171].

The authors have suggested that strict adherence to a gluten-free diet (the questionnaire survey documented that 97.7% of the patients with dermatitis herpetiformis adhered to a gluten-free diet), less smoking and less hypercholesterolemia played a role in the observed substantial health benefit.

5.2. Gluten Ataxia and Neurological Phenotypes in Gluten-related Disorders

In the diagnosis of gluten ataxia cases formerly known as "idiopathic sporadic ataxia" accompanying circulating antibodies against gluten, are included. It is a type of cerebellar ataxia caused by exposure to gluten in sensitive patients and may complicate celiac disease but also other gluten-related disorders[172]. In the USA and Europe gluten ataxia may occur in 24% of patients with cerebellar ataxia[173] but it was considered to be rare in Asia. Japanese neurologists have recently speculated that more than 10% of cerebellar ataxia patients in Japan, have gluten ataxia[174].

The most common clinical form of presentation is the typical pure cerebellar ataxia with abnormal gait and balance, and associated dysarthria. Less frequently as a clinical form of diffuse or focal myoclonus manifestations. It may be accompanied by nystagmus and other ocular signs, over 70% of cases. It usually has a slow start and generally affects individuals older than 50 years without difference between both sexes. A rapid progressive disease may occur but a slow evolution, with a stationary clinical course, punctuated by some transient worsening episodes is seen. In most cases, there is a long previous history of several digestive symptoms of recurrent characteristics, but some patients have not been previously diagnosed as suffering from celiac disease or non-celiac gluten sensitivity. In the majority of patients with gluten ataxia, magnetic resonance imaging of the brain shows the presence of a moderate cerebellar atrophy, mainly in the cerebellar vermis. The Sheffield´s group directed by Dr. Hadjivassiliou, was the first to describe this type of association and has made great contributions to this field[175].

The diagnosis of gluten ataxia is confirmed by the presence of anti-gliadin antibodies (AGA)[176], and anti-tTG-2 and anti-tTG-6 when available. Patients

with gluten ataxia have anti-tTG-2 IgA in less than 40%. When combined with anti-tTG-6 it can reach a positivity of up to 85%[175]. Autoantibodies to tTG-6 have been identified in immune-mediated ataxia in patients with gluten sensitivity, thus suggesting a critical role for transglutaminase 6 in cortical and cerebellar neurons[177,178]. Sometimes gluten ataxia has a familial character with several first-degree members affected[179].

Gluten ataxia is therefore considered an autoimmune disease characterized by the presence of a cerebellar injury, affecting mainly Purkinje cells[180] that produces ataxia. It has been found that there is cross-reactivity between antigens located at the level of Purkinje cells and circulating antibodies related to gluten. The deposits are confined not only to the cerebellum, but also in the pons and spinal cord.

These patients must be treated with a strict gluten-free diet maintained during a life-time. After 1 year of starting the gluten-free diet, stabilization or improvement of clinical signs of ataxia, are good indicators or the confirmation that the patient indeed suffers from gluten ataxia. The degree of response clearly depends on the time elapsed since the start of the occurrence of ataxia and the establishment of the gluten-free diet. If the gluten-free diet is started after the first six months of the diagnosis the improvement is more favorable.

It is important to remember that nutritional deficiency and coexisting autoimmunity may cause neurologic dysfunction in celiac disease. A variety of neurologic phenotypes with different etiologies were found 68 patients with either celiac disease or AGA positive non-celiac disease in a 10 year period (2002-2012): cerebellar ataxia, neuropathy, dementia, myeloneuropathy, autoimmune disease, deficiencies of vitamin E, folate, or copper, genetic disorders, toxic or metabolic syndrome. The authors concluded that gluten exposure may produce neurologic dysfunction even in those patients without established celiac disease[181].

6. Associated Diseases

6.1. Celiac Disease and Type-1 Diabetes Mellitus

The association between type-1 diabetes mellitus and celiac disease has been known since the 1960s. The first reports in adults came from the United States by Ellenberg and Bookman in 1960[182], Vinnik et al.[183] and Green et al. in 1962[184], all cited by Wruble and Kalser[185], who also observed that diabetic steatorrhea is uncommon but a more intense manifestation of diabetic diarrhea. The amount of fecal fat is significantly higher that the observed in cases of celiac disease. According to Wruble and Kalser, Thompson observed 2 cases of diabetes in 119 patients with celiac disease and reported an increased incidence of diabetes in relatives of patients with celiac disease[186]. However Carter et al. could not confirm the familial association between diabetes mellitus and celiac disease[187]. But these were the early days in the diagnosis of atypical celiac disease and the genetics of both conditions was still unknown.

In children, the first cases with celiac disease and type-1 diabetes mellitus were reported in 1969[188-190].

A controlled longitudinal follow-up study of 10 years of progression in 335 celiac adult patients diagnosed in 1980-90 compared with age- and sex-matched control patients with various gastrointestinal symptoms, found a high statistical significant prevalence of endocrine disorders in patients with celiac disease (11.9% in celiac patients and 4.3% in the control group, $p<0.003$)[191, 192]. More recently, other authors found a prevalence of 5.4%-7.4% of type-1 diabetes mellitus in patients with celiac disease [71,193].

The high prevalence of the existence of both diseases can be explained in part by the sharing of common markers for the genetic susceptibility within and outside the HLA system. HLA-DQB1*0201 allele (part of the HLA-DQ2 heterodimer) was present in 17 of 18 patients (94%) with both diseases in Finland[194]. It should be taken into account that during a screening study, most children do not complain of digestive symptoms. Nevertheless, many have retarded growth and some other signs or symptoms of celiac disease, such as delayed puberty, hypertransaminasemia, and/or chronic iron

deficiency anemia, arthralgias, and dental enamel defects[195-198]. Recent studies of genome wide association have found additional genes that are shared by celiac disease and type-1 diabetes mellitus. Both diseases are polygenic in nature and several loci in different chromosomes determine their susceptibility. Since both are T cell mediated diseases, those genes regulating the immune response are likely to be shared and explain their familial association[199-202].

The diagnosis of type-1 diabetes mellitus was established in 90% of children before celiac disease was recognized[191]. The patients with diabetes mellitus and symptoms associated with celiac disease who follow a gluten-free diet notice an overall clear clinical improvement, in children often an increase in the rate of growth, increased hemoglobin levels. There is improvement in the control of diabetes mellitus, as supported by reduced hypoglycemic episodes and daily needs of required insulin[192,203].

More than 5% of patients with type-1 diabetes mellitus have also celiac disease confirmed by the histopathological features of duodenal biopsy specimens and response to gluten-free diet. This strong association between the two diseases would support the systematic screening of celiac disease among patients with insulin-dependent diabetes. Strategies for follow up include periodical serological determinations of specific antibodies, initially at diagnosis, followed by every six months during the first year and repeated at least annually, for five or more years. Patients with specific positive serological tests and with the presence of the genetic markers of susceptibility (HLA-DQ2 and/or HLA-DQ8) require a duodenal biopsy to confirm the diagnosis. Although there are many clinical guidelines that recommend screening implementation, in particular in children, in adolescents and young adults, its application in clinical practice has failed to achieve the desired levels of performance and expectation[204-206]. The American Gastroenterological Association does not recommend to screen all type-1 diabetes mellitus because those without symptoms are not motivated to follow a gluten-free diet and the natural course of asymptomatic celiac disease is unknown[207].

Also no ideal serological technique is available for screening. The best at present are the antibodies against tTG and anti-endomysium antibodies (EmA). The main problem is that the tests for specific antibodies are very sensitive (80%-90%) only in the presence of villous atrophy, but have a low diagnostic sensitivity (10%-30%) in Marsh stages 1 and 2 celiac patients. AGAs have virtually been abandoned for the diagnosis and screening of celiac disease since these antibodies have a low sensitivity and specificity[208,209].

In spite of these shortcomings, the cost of establishing a screening program for celiac disease in patients with type-1 diabetes mellitus is moderate. Assuming that the average prevalence of diabetes mellitus is 0.4% in the general population, for a hospital that serves a population of 200,000 people, about 800 patients would have to be screened. A determination of tTG antibodies costs about 8 euros per determination. Positive cases would have to undergo an endoscopy with duodenal biopsies. The average cost of this procedure is 300 euros per patient. At present, therefore in well-equipped hospitals it can be concluded that the costs for screening are acceptable and should be recommended in symptomatic cases suggesting the presence of celiac disease. In these situations an early diagnosis of celiac disease will prevent a series of unnecessary expenses with less discomfort for the patient on the short term and the prevention of osteoporosis and possible malignancy at a later stage. A recent meta-analysis analyzed the prevalence of celiac disease in 26,605 patients with type-1 diabetes mellitus in different countries. The mean prevalence of biopsy-confirmed celiac disease was 6% (95% CI, 5.0% to 6.9%). However, the heterogeneity observed was large. The prevalence in adults with type-1 diabetes mellitus was 2.7%. In mixed populations with both children and adult diabetic patients the prevalence was 4.7% and the prevalence of children with diabetes mellitus was 6.2% ($p<0.001$). More than one in twenty patients with type-1 diabetes has biopsy-verified celiac disease. The authors concluded that this prevalence is high enough to motivate screening for celiac disease among patients with type-1 diabetes mellitus[205].

A Swedish study has identified that the major histocompatibility complex class II transactivator (CIITA) gene (16p13) is associated to celiac disease and type-1 diabetes mellitus in families and is age dependent[200].

This suggests that advances in human genome and the identification of genes regulating the immune response may help to identify the heterogeneity of the clinical observations in both diseases.

6.2. Thyroid Diseases and Celiac Disease

Celiac disease has been found to be present at an increased rate in patients who have an autoimmune thyroid disease (Grave's disease and Hashimoto's thyroiditis), with a prevalence ranging from 2% to 7%[210-213]. Similar observations have been made in patients with celiac disease, in whom serological signs of autoimmune thyroid disease were present in up to 26%. Occurrence of thyroid dysfunction was detected in up to 10% and the risk of thyroid disease was estimated to be 3-fold higher as compared to controls[214-217].

It has been reported that celiac individuals who are following a gluten-free diet may still develop autoimmune thyroid impairment, suggesting that gluten withdrawal does not protect them in this respect[218,219]. By contrast, the decrease of the thyroid antibodies after 2 or 3 years[220] or the normalization of thyroid function after 1 year of gluten-free diet has been reported in other studies[221]. These different results may depend on longer duration of gluten-free diet in treated patients with celiac disease[222]. The authors prospectively evaluated the presence of thyroid autoimmunity in children and adolescents with celiac disease on a gluten-free diet. At the end of the 2 years follow-up, an increase of 7% in the prevalence of patients with celiac disease with thyroid autoimmunity requiring L-thyroxine was found. Apparently, thyroid autoimmunity is no more common in pediatric and adolescent patients with celiac disease on a gluten-free diet than in the control group. Since its clinical development does not seem to impact on growth, the authors concluded that a long-term regular screening program for thyroid disease may not be necessary for all patients with celiac disease on a gluten-free diet, but only for those who are suspected of having thyroid diseases[222].

Increased prevalence of celiac disease, autoimmune thyroid disorders, and type-1 diabetes mellitus, has been widely reported[223]. However, the authors have also concluded that certain patient groups such as those with autoimmune diseases may be offered screening but active case finding seems to be the most prudent option to follow in most clinical situations. In these cases such associations may lead to adverse effects on the growth, metabolism and fertility, so early detection is necessary to prevent secondary complications of these disorders.

The coexistence of celiac disease and autoimmune thyroid disease has been explained by several mechanisms such as common genetic predisposition and the association of both diseases with the gene encoding cytotoxic T-lymphocyte-associated antigen-4, a gene conferring susceptibility to thyroid autoimmunity. In addition, it has also been demonstrated that tTG-2 IgA antibodies react with thyroid tissue, and this binding could contribute to the development of thyroid disease in celiac disease[224].

7. Malignancy Associated with Celiac Disease

Gluten-free diet is demonstrated as an efficient treatment for the vast majority of celiac patients, leading to normalization of clinical and biochemical disturbances, reversion of inflammatory changes in the small bowel mucosa, and restoring the normal villous architecture. However, many celiac patients remain undiagnosed for several years before an adequate treatment. Additionally, the treatment of celiac disease with a lifelong strict gluten-free diet is difficult to follow, and an inadequate adherence rate of around 30% has been repeatedly reported[225-227].

The presence of gluten cross-contamination should also be considered in patients with persistent symptoms and/or villous atrophy[228,229]. These factors contribute to persistent inflammation with consequent malabsorption of micronutrients, and increased risk of infection, which may explain an excess of mortality and a higher malignancy risk among the celiac population[230,231]. The association of celiac disease with an increased risk for several malignancies has

been repeatedly reported in the medical literature of the last decades. This association is particularly clear in the case of a specific subtype of non-Hodgkin lymphoma, the enteropathy-associated T cell lymphoma which is considered as an established complication of celiac disease[232]. However, controversy exists regarding the increased risk of other neoplasias among patients with celiac disease, including solid tumors.

7.1. Overall Risk of Malignancies in Patients with Celiac Disease

The risk of malignancy in patients with celiac disease has been evaluated in several large epidemiological studies carried out in European and North American populations[232-235], as well as a systematic review with meta-analysis of 3 prospective studies that included 35,582 individuals[236]: According to the authors, the overall risk of presenting any neoplasia among patients with celiac disease was not increased compared to control populations, with a pooled OR of 1.07 (95% CI, 0.89 to 1.29). Relevantly, no significant heterogeneity or publication biases were observed in this meta-analysis. Although celiac patients are at a slightly increased risk of mortality, this cannot be attributed to malignancy in general[236].

7.2. Lymphoproliferative Malignancies of the Small Intestine

Several population based studies have repeatedly found a 2 to 6-fold increased risk of small bowel lymphoproliferative malignancies in celiac disease[237], particularly due to non-Hodgkin lymphoma. A recent meta-analysis summarizing the results of 8 individual cohort and case-control studies has estimated a pooled OR of 2.75 (95% CI, 2.0 to 3.78) for this neoplasia in celiac patients[236].

The highest non-Hodgkin lymphoma relative risk in celiac disease has been described for T-cell non-Hodgkin lymphoma, a particular subtype repeatedly related with celiac disease. The risk estimates for T-cell non-Hodgkin

lymphoma have varied markedly in the literature, and has been summarized with a pool OR of 15.84 (95% CI, 7.85 to 31.94) in a meta-analysis[236].

The increased risk of lymphoproliferative malignancies in celiac disease has been directly related with persistence of chronic inflammation. A multicenter retrospective cohort study demonstrated that the risk of small intestine lymphomas in celiac disease was dependent on small intestinal histopathology, and patients with villous atrophy (Marsh 3 stages in duodenal/jejunal biopsies) had a statistically significantly higher risk of lymphoma than those celiac patients with either Marsh 1 to 2 or Marsh 0 but positive celiac disease serology[234]. The degree of inflammation is then crucial for the development of lymphoproliferative malignancies in celiac disease, as recently shown also for rheumatoid arthritis, in which disease activity and not suppressive treatment was demonstrated as the underlying cause of neoplasia development[238].

The protective role of gluten-free diet in reducing the overall malignancy risk appeared after 5 years of following the diet[239]. A large study found an overall risk of lymphoproliferative malignancies of 2.82 (95% CI, 2.36-3.37) that decreased to 2.25 during 1 to 5 years of follow-up after celiac disease diagnosis and further to 1.98 after more than 5 years of follow-up[234].

On the other hand, individuals with celiac disease and lymphoproliferative malignancies were at an increased risk of death compared with individuals with lymphoproliferative malignancy only. But the increased mortality has been observed in the first year after the diagnosis of lymphoproliferative malignancies in celiac disease patients, which has been related to the predominance of T-non-Hodgkin lymphoma in that population. Thus there is no evidence that co-existing celiac disease influences survival in individuals with lymphoproliferative malignancy[240].

7.3. Small Bowel Carcinoma Risk in Patients with Celiac Disease

Malignant tumors of the small bowel are rare neoplasms comprising only 3% of all gastrointestinal tumors; approximately 25% of which are small bowel adenocarcinomas. Identified risk factors for small bowel adenocarcinoma

include Crohn's disease, celiac disease, and genetic polyposis syndromes[241]. Since the first report of association between small bowel adenocarcinoma and celiac disease in 1958[242], more cases have been reported[243]. Most of the population based epidemiological studies have shown that, although rare, the incidence of small bowel adenocarcinoma in celiac disease is increased between 4- and 11-fold compared to matched control populations[233,235,244].There were no differences among genders[235]. In a 30-year population based study in Finland no increase in the prevalence of small bowel carcinoma was found, possibly due to the overall rarity of this neoplasia. In this study, non-Hodgkin lymphoma emerged in patients with undiagnosed or poorly treated celiac disease[245].

7.4. Colorectal Cancer and Celiac Disease

The risk of colorectal cancer among patients with celiac disease has been evaluated in various reports during the last decade. The first report on this topic specifically assessed the prevalence of colorectal neoplasia (including tubulo-villous adenomas and carcinomas) among older patients with celiac disease who presented with iron deficiency anemia or an altered bowel habit[246]. In this report, a high prevalence of colorectal cancer was demonstrated in older patients presenting with iron deficiency anemia or an altered bowel habit. The prevalence was not superior to that of non-celiac patients with the same presentations. In a parallel study, the incidence of colorectal cancer among Swedish patients hospitalized with celiac disease and dermatitis herpetiformis was assessed in a retrospective population-based study[233]. The authors concluded that the risk of colorectal cancer was slightly increased, mainly in the ascending and transverse colon standardized incidence ratio (SIR) was 1.9 (95% CI, 1.2 to 2.8) among the group of patients with celiac disease, but not in those with dermatitis herpetiformis. Remarkably, an increased risk of rectal cancer was not found for both gluten-related diseases. A recent population based study has also corroborated this increase in the risk of colorectal cancer among celiac patients[235], but to a

lesser extent than the previously reported (SIR was 1.35; 95% CI, 1.13 to 1.58)[247].

In contrast, other studies such as carried out in Scotland[244], Finland[245], United States[248], Canada[249], and Argentina[250,251] have failed to demonstrate an increased incidence of colorectal cancer among patients with celiac disease and dermatitis herpetiformis. Most interestingly, recent research has also identified that the risk of colorectal cancer among Italian patients with celiac disease was even lower than for the general population, with a SIR of 0.29 (95% CI, 0.07 to 0.45)[252].

The discrepancy observed among different epidemiological studies on a possible increased risk of colorectal cancer in subjects with celiac disease when compared with the respective matched control populations may be attributed to a different diet composition and genetic background of the population studied. However, the possible increase in the risk of presenting colorectal cancer in the celiac population can be considered marginal, and do not support specific preventive measures for these patients, different to those established for an average risk general population. In fact, a prospective research aimed to evaluate the yield of colonoscopy for diagnosing additional pathologies in celiac patients on a gluten-free diet and with a newly diagnosed iron deficiency anemia or persisting diarrhea did not demonstrate an increased prevalence of colonic neoplasia regarding control subjects[253]. These authors have concluded until new data becomes available that colonoscopy should be considered in patients with celiac disease (over the age of 45 years) who present with iron deficiency anemia. Whilst, for celiac disease patients with persisting diarrhea (on a gluten-free diet) in the absence of sinister symptoms, a flexible sigmoidoscopy may be the initial investigation in order to exclude microscopic colitis.

In any case, the importance of a strict adherence to a gluten-free diet in preventing colorectal neoplasia has been recently highlighted. A low adherence to a gluten-free diet was an independent factor significantly associated with the presence of colonic adenomas (OR 6.78; CI, 1.39 to 33.20)[251], and those

patients who had a strict adherence to a gluten-free diet showed additional reductions in the risk of presenting colorectal cancer[252].

7.5. Breast Cancer in Women with Celiac Disease and Other Hormone-Dependent Neoplasm

Several population-based cohort studies have repeatedly shown a reduction in the risk of breast cancer development among women with celiac disease compared to matched controls[232,233,235,254-256], with SIR ratios varying from 0.3 to 0.85. This reduction in breast cancer risk has been explained by malnutrition and weight loss, associated with clinical or subclinical nutrient deficiency[145] and the presence of various reproductive disturbances in women with celiac disease, including delayed menarche, early menopause and ovulatory dysfunction[257-259]. These disturbances contribute to limit the lifetime exposition to sex hormones that are implicated in the etiological role for breast cancer.

Estrogens also play an important role in promoting endometrial and ovarian cancer, but in contrast with breast cancer, parallel reductions for these last cancers have not been universally demonstrated among women with celiac disease. Available studies show opposite results[233,235,260].

7.6. Thyroid Cancer and Celiac Disease

The association of celiac disease with thyroid disease, especially autoimmune thyroiditis, is widely recognized[261] as has been described early in this chapter. Few studies have also tried to relate celiac disease with papillary thyroid cancer, providing an increased risk between 2.5[262] and 22.52 fold[263]. In contrast, some other cohort studies from Sweden have not demonstrated such association[233,264].

7.7. Esophageal Cancer

An increased risk for esophageal cancer, especially squamous carcinoma, in celiac disease was described in the early literature[265,266], but has not been reproduced in later published well-designed research studies[235,245].

7.8. Preventing Cancer in Celiac Disease

Delayed diagnosis of celiac disease has shown to increase cancer risk because of the prolonged period of dietary exposure to gluten[267]. This risk is more relevant for the intestine -specific cancers such as small bowel carcinoma and non-Hodgkin lymphoma. Except for lymphoproliferative malignancies, no definitive data support an increased risk of cancer in patients with celiac disease, thus, surveillance and preventive measures for this population are currently not justified. However, the benefits of a gluten-free diet in reducing the overall risk of cancer must be emphasized. For many years it is known that following a gluten-free diet during an extended period reduces the risk of cancer to the level of a control population[239]. The long-term risks of malignancy beyond 10-15 years in people with celiac disease diagnosed in the Lothian region of Scotland, United Kingdom showed that the risk of any malignancy in celiac disease patients compared with the general population was increased 40% (SIR = 1.41; 95% CI, 1.09 to 1.78]. The increased risk for cancer overall persisted for up to 15 years, beyond which no overall increase in malignancy risk was observed, although the risk of non-Hodgkin's lymphoma remained raised beyond 15 years (SIR = 5.15; 95% CI, 1.40-13.2)[244]. Long-term risk studies beyond 25 years of follow-up are needed. For the time being, the above observations provide further support to strongly advise all patients with celiac disease and dermatitis herpetiformis to adhere to a strict gluten-free diet for life.

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