



A REVIEW OF ITS ETIOLOGY, PATHOGENESIS AND ASSOCIATED DISEASES (PART 1)

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Definition

Celiac disease (CD) is defined as a permanent intolerance to gluten. It is an autoimmune condition that appears in genetically predisposed subjects. It is prompted and maintained by the consumption of cereals containing gliadins or prolamins, which are present in wheat, barley, rye and oats (1,2).

Historical antecedents

The first descriptions of the disease were made in the second half of the 2nd century BC by the Greek physician, Areateus de Cappadocia, from Asia Minor. His works were published in England in 1856 by Dr Francis Adams.

The Greek word *koliakós*, from which the disease derives its name, means "those who suffer with their abdomen".

In 1888, twenty-one centuries after Areateus' original description, the English physician Samuel Gee, reported the clinical condition of CD in children and adults, providing the first classic description of the disease.

After the Second World War, a crucial advance was made and described in great detail by the Dutch pediatrician Dr Dicke, who published his doctoral thesis at the University of Rotterdam in Holland in 1950. He conclusively demonstrated that celiac children experienced an extraordinary improvement when foodstuffs containing flour from wheat, barley and rye were excluded from their diet.

Shortly afterwards, in 1954, Dr Paulley, an English physician, reported the characteristic histological change of the small intestine, after studying material from a "surgical" intestinal sample obtained from a celiac patient. This was the first time the presence of intestinal villous atrophy was described as being a lesion characteristic of CD (3).

Etiology

The medical physicians Van de Kamer and Dicke discovered that gluten, a protein present in wheat flour, was the principal toxic agent responsible for CD (4).

Gluten is the protein fraction of wheat and related cereals. It may be fragmented into ethanol-soluble gliadins and prolamins, and insoluble glutenins in the same. They are the main causes of toxicity in the intestinal mucosa, although recent studies suggest that glutenins can also damage it. Common to all the gliadins of wheat is their high glutamine and proline content, while those of maize and rice have a low content of these aminoacids. This particular aminoacid composition confers a distinct capacity to stimulate the immune system markedly. The wheat gliadins can be separated by

electrophoresis into four fractions, known as α , β , γ and δ . All of them have a toxic capacity in the intestinal mucosa, but the α fraction may be mainly responsible for the disease. This peptide, comprising 33 aminoacids, is resistant to the degradation of the enzymes in the stomach and pancreas, and the proteases of the human intestine, and is unaltered after the digestion of the gluten (5).

Epidemiology

CD is one of the most prevalent chronic illnesses worldwide (one case per 100-200 individuals), although only 20-50% of them present symptoms (6).

It has been postulated that the condition predominantly affects white Europeans, although it has also been described in Arab populations, and there are some studies of its incidence in Asia and India (7), and in China and sub-Saharan countries. It is a very common illness throughout the world, except in Japan and China. The populations of these latter two countries are characterized by a very low prevalence of the HLA-DQ2 genotype, which is important for hereditary transmission, and a low level of consumption of cereals containing wheat, since their diet is principally based on rice, which partially prevents the appearance of the disease.

Epidemiological studies based on case records underestimated the real frequency of the disease, since they included patients who had already been diagnosed, fundamentally with the classic forms of infant CD. It was subsequently observed that more cases were being identified in adults, as were oligosymptomatic forms, with extra-digestive manifestations, and even asymptomatic cases (8). Thus, in our study, 60% of patients with CD were diagnosed in adulthood (9).

In Spain, at least one in 389 people in the general population exhibits CD (10), which is a similar rate to that reported in other European and American countries (11-15).

Screening studies of CD in the general population have revealed a high prevalence of the disease (one per 100-200 people), and low levels of diagnosis (16).

An Italian study of schoolchildren aged between 6 and 15 years, with a screening protocol that included antigliadin and antiendomysial antibodies, and duodenal biopsy of those who tested positive in the two screenings, found a prevalence of one in 184 (17).

Studies of Saharawi children showed a high frequency (5.6%) of CD in that population, which could be related to the high level of consumption of cereals, since their diet is based on wheat flour, as well as to a stronger genetic disposition (18).

A recently published Swedish study found that the prevalence of symptomatic CD decreased after the dietary recommendations were introduced in 1996, but no differences could be found in the cases of CD not diagnosed following the screening of the newborn, before and after 1996 (19).

Pathogeny

The first publication about the family nature of CD dates from 1935 (20). Currently, we know that there is 75% concordance for CD between monozygotic twins compared with 11% for dizygotic twins (21), which is evidence of the disease's heavy genetic load (22,23).

There is a strong association with HLA-DQ2, whose pathogenic involvement has been widely demonstrated.

The strongest genetic association is with the haplotypes DR3-DQ2 and DR5/7-DQ2 of the class II HLA system. The molecule DQ2 is an / heterodimer that is expressed on the surface of B lymphocytes, activated T lymphocytes and antigen-presenting cells. This molecule is encoded by the alleles DQA1*0501 and DQB1*0201 (24), which are normally inherited on the same chromosome (*cis* inheritance) within the DR3-DQ2 haplotype. It is also possible that they are inherited on different chromosomes (*trans* inheritance) in the DR5-DQA1*0501 and DR7-DQB1*0201 haplotypes. The final result is the same – the formation of the heterodimer HLA-DQ2 with an ALPHA1*0501 chain and another BETA1*0201, which confer susceptibility to CD (25).

From 2 to 10% of those with the disease are HLA-DQ2-negative; most of them have in common the presence of the DQ8 heterodimer (26), which exhibits certain characteristics of the peptide-binding cleft, similar to the DQ2 heterodimer (27).

However, the DQ2 haplotype is also present in 20-30% of the general population (28), as demonstrated by the necessity for other genetic or environmental factors that are responsible for the development of the disease. Thus, it has been observed that within the class I HLA gene the MICA 5.1 allele is associated with non-classic forms of CD in subjects containing the high-risk DQ2 heterodimer (29,30). This gene can be protective or may modulate the phenotypic expression of CD in celiac patients, doing so to the same extent in DQ2-positive and DQ2-negative cases. The functional role of MICA in the pathogenesis of CD is yet to be ascertained (31).

The risk of developing typical forms of CD is associated with the DR7/DQ2 haplotype, and B8/DR3/DQ2 is significantly more frequent in atypical patients. In these, the MICA A5.1 allele confers an additional effect on the DR3/DQ2 haplotype that may modulate the development of the disease. The MICA gene does not appear to be involved in the susceptibility towards suffering from CD, but does seem to play an important role in the development of the various forms of the disease. MICB also appears to influence the various polymorphisms of CD (32).

T cells are present in normal intestinal mucosa, both in the lamina propria and between the enterocytes (intraepithelial lymphocytes, or IELs). In the epithelia of the intestinal mucosa of a celiac patient exposed to gluten the populations of TCR alpha/beta, CD8+ and TCR gamma/delta are expanded, all expressing the marker of Ki67 proliferation. When the gluten-free diet (GFD) was established, the IELs of the TCR alpha/beta CD8+ type returned to normal, while the gamma/delta IELs remained at permanently high levels (33).

The lymphocytes of the lamina propria are of the CD4+ type and recognize the gliadin expressed along with the HLA-DQ2 heterodimer on the surface of the antigen-presenting cells. All these IEL populations, once activated, are capable of producing a large number of cytokines with cytolytic potential, above all IFN-gamma, IL-2, IL-6 and TNF-alpha (34). Additionally, the presence of characteristic markers reveals that some of these lymphocytes could be activated cytotoxic T cells, which would contribute to

mucosal damage (35).

The next step in the evolution of the disease would be the infiltration of the lamina propria by alpha/beta+ TCR lymphocytes, most of which are CD4+ and have a memory cell phenotype (CD45RO+) (36).

The acidic pH of the stomach is without doubt an important cause of deamination but the tissue transglutaminase (tTG) enzyme is mainly responsible for this process in the mucosa of the small intestine. A raised level of activity of this enzyme has been noted in the mucosa of celiac patients (37).

tTG appears to induce controlled deamination of the residues of gliadin, in contrast to that produced spontaneously, which specifically affects those that are crucial for the effective anchoring of the peptides to the DQ2 molecule (38).

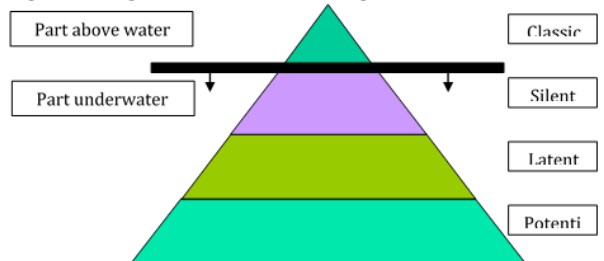
Thus, the pathogeny of CD appears to be directly related to the immune response to peptides derived from gliadin that are rich in glutamine residues, and which have been previously deaminated by tissue transglutaminase.

Spectrum of gluten intolerance

CD, or enteropathy due to gluten sensitivity, is characterized by the great heterogeneity of its forms of clinical presentation.

On the basis that CD can manifest itself in many clinical and histological forms, Logan (39) drew an analogy between gluten sensitivity and an iceberg, whereby the part above the water is equivalent to the classic forms of the disease, while the part below the water is like the so-called silent, latent and potential atypical forms (40).

Fig. 1. The Logan Celiac Disease iceberg



- **Classic or symptomatic forms:** These are accompanied by symptoms of malabsorption and arise in genetically predisposed subjects.
- **Silent or asymptomatic forms:** These differ from the previous type in that they can take an asymptomatic form, or exhibit discreet symptoms (ferropenic anemia) or extra-intestinal symptoms (cryptogenic hypertransaminasemia, dermatitis herpetiformis, osteopenia, depression, etc.). The better understanding of the extra-digestive manifestations of the disease, and the search for cases within risk populations (first-degree family members and diabetic juveniles) mean that increasing numbers of patients are being diagnosed with this form of CD.
- **Latent forms:** These are exhibited by people who have a normal intestinal biopsy with a gluten free diet and villous atrophy induced by gluten at another time during the evolution of the disease. It may be suspected in subjects with positive antiendomysial antibodies and normal histology, or with an increase in intraepithelial antibodies, which carry the type and T receptors, or with a pattern of antibodies in the lumen similar to that of CD. These subjects may exhibit a minor or initial form of the disease.
- **Potential forms:** These affect apparently healthy individuals, and as such have a normal intestinal histology throughout their lives.

Other classifications are currently used in which patients who have a clear digestive symptomatology, with chronic diarrhea and intestinal malabsorption are considered classic forms of the disease. Oligosymptomatic or asymptomatic patients are grouped together as atypical forms (41).

Some studies demonstrate that the risk of suffering typical forms of CD is associated with the DR7/DQ2 haplotype, and the presence of B8/DR3/DQ2 is significantly raised in patients with atypical forms of the disease. In these, the MICA-A5.1 allele confers an additive effect on the DR3/DQ2 haplotype, which could condition the development of the disease (42,43).

Clinical presentations

CD may present at any age and in an approximate proportion of 2-3 women for each man. The majority of epidemiological studies have shown a greater prevalence in children than in adults (44), but this situation has been changing in recent years to the point where, currently, more adult patients are being diagnosed, and up to 20% of celiac patients are over 60 years of age at the time of diagnosis (45).

The clinical manifestations of CD differ across the age groups. Babies and young children (under 2 years), generally present with diarrhea, abdominal distention, vomiting, irritability, anorexia, and constipation. Older children and adolescents usually present with extra-intestinal forms, such as stunted growth, neurological symptoms, or anemia. When the disease is florid, it usually manifests itself as a combination of diarrhea, weight loss, pain and/or abdominal discomfort, nausea and vomiting, flatulence, meteorism, asthenia and general weakness.

The frequency of bowel movements and the nature and consistency of the stools are very variable. In general, patients who present extensive intestinal affection have 4-10 bowel movements daily that are soft or mushy and malodorous. However, patients may present with diarrhea, and some even have marked constipation.

The sensation of abdominal distention is very frequent and accompanied by intense discomfort, with difficulty passing retained gases. Those suffering this commonly have digestive intolerance, manifested in the form of nausea and/or occasional food vomiting.

Weight loss of patients with CD generally depends on the severity and extent of the intestinal lesions, and on the capacity of the patient to compensate for the losses due to intestinal malabsorption by increased caloric intake. Some patients with significant affection have a good appetite and are capable of maintaining a stable weight (47) or present only a slight associated loss of weight. In cases of severe disease, this may be associated with a certain degree of anorexia, which is usually accompanied by a rapid and pronounced loss of weight.

Children and young people affected by CD exhibit stunted growth which, on occasion, may be very pronounced.

In most celiac patients, the observed weakness, lassitude and tiredness are a consequence of the frequent discomfort and the associated ferroplenia or anemia, and the hypopotassemia and hypocalcemia that accompany it.

Abdominal pain may be defined as a persistent and diffuse discomfort that is predominantly peri-umbilical and epigastric, related to the retention of accumulated gases. It is accompanied by prominent abdominal distention in many cases, in which it produces great discomfort, even causing a very intense colic-type pain.

The classic or digestive forms are not the most frequent forms of CD, accounting for only 30-50% of cases; the remainder are silent or subclinical forms.

Associated diseases

Clinical diagnosis

Some decades ago, CD was thought fundamentally to occur in children, given the presence of an intestinal malabsorption syndrome. Since then, there has been an increase in the oligosymptomatic and asymptomatic forms noted, and a high percentage of adult individuals have been found to have the disease. This has occurred as a consequence of our better understanding of the wide clinical spectrum of the process. On the other hand, although the different risk groups and the processes associated with CD are better identified, latent and silent forms are being diagnosed in increasing proportions. The most habitual clinical forms in which the disease presents itself are considered below.

- **Classic:** Characterized by a syndrome of malabsorption, and occurring in children aged 2 to 5 years. It is the most frequent form of presentation in infancy. In adults, the appearance of chronic or intermittent diarrhea, with weight loss, should lead to a suspicion of the illness.
- **Early onset:** This is very infrequent and occurs in children under 2 years of age, following the introduction of gluten into the diet. Breastfeeding delays but does not prevent the appearance of the disease.
- **With non-specific digestive symptoms:** This form may manifest itself only as flatulence, or as nonspecific diarrhea in children, or irritable bowel syndrome in adults, even with constipation.
- **Non-classic or extra-digestive:** These are subjects with extra-intestinal manifestations, or with not very striking digestive symptoms.
- **Silent or asymptomatic:** These are diagnosed above all in subjects belonging to groups at risk of having the disease.

Currently, cases that feature a predominance of digestive symptoms are classified as classic or typical forms of CD, and atypical forms, which feature a predominance of extra-digestive symptoms (42).

CD takes many forms in its clinical presentation. It is relatively easy to consider CD as a diagnosis when there are digestive symptoms present, but not when they are absent (48). For this reason, it is useful to have a good understanding of its extra-intestinal manifestations (Table 1).

Associated diseases (Table 1)

Cutaneous manifestations: Dermatitis herpetiformis

Dermatitis herpetiformis (DH) was first described in 1884 by Louis Duhring (49) and is classified, along with pemphigus and the pemphigoid, within the group of bullous diseases. Currently, it is considered the cutaneous manifestation *par excellence* of gluten sensitivity. The characteristic symptom is an intense pruritis that can take variable forms of presentation, from vesicular papules with excoriations to eczematous or minimal erythema and purpura (50).

In reality, DH and CD are two phenotypic manifestations within the gluten sensitivity spectrum, their immunogenetic basis being the same. Thus, a high percentage of DH is found among intestinal biopsies of family members of DH patients (51).

DH is more common among young males, appearing above all in subjects of Caucasian origin. The characteristic lesions are blisters, urticarial plaques and excoriations. These are very itchy, and usually have a symmetrical distribution, particularly in the areas where rubbing occurs, such as the extensor surfaces of the elbows, the waist and buttocks, and the extensor surface of the knees.

From a clinical point of view, it tends to present a chronic recurrent course in which spontaneous remission occurs in only 10-15% of cases. The diagnosis is made by a biopsy of the unaffected skin from around the lesions and the demonstration by fluorescence

microscopy of the presence of granular or fibrillar deposits of IgA at the level of the dermal papillae or just below the basal membrane. The initial lesion consists of the appearance of neutrophilic microabscesses at the level of the aforementioned papillae (52).

In DH the intestinal lesion is habitually of low intensity, and villous atrophy is found in up to two-thirds of cases, although this is usually asymptomatic from the digestive point of view. The serology of CD is usually positive, although with lower percentages than in other forms of presentation.

DH responds rapidly, although in a transitory manner, to pharmacological treatment with dapsones, and slowly, but definitively to a GFD. It presents in 25% of patients with CD and its presence is an unequivocal sign (100% certainty) of the existence of an associated CD.

Lesions of the oral mucosa, such as cold sores and cracked skin, alopecia areata and vitiligo, occur more frequently in patients with DH than in the general population. Thus, in 1995, Corazza (53) reported the association between alopecia areata and CD for the first time. Prospective serological screening of 256 patients with alopecia areata revealed the existence of three cases of CD, each of which was asymptomatic from a digestive point of view. However, other studies, such as that of Bardella (54), found no effect of the suppression of dietary gluten on hair growth in these patients.

The association of CD with psoriasis is controversial (55). Some authors have found that 16-30% of patients with psoriasis have CD antibodies, half of whom present an enteropathy of distinct intensity (56). Withdrawing gluten from the diet improves the cutaneous manifestations of the disease, including in cases with minor intestinal lesions or those with none.

Osteoarticular pathology

Osteopenia and polyarteritis (57) are extra-digestive manifestations of EC. Osteoporosis can only be correctly evaluated by bone densitometry (58). Arteritis in CD may be peripheral, axial or combined, and is present in up to 25% of celiac patients (59).

Bone demineralization and joint pain are both improved in a sustained manner by treatment with a GFD.

Reproductive disorders

The risk of spontaneous abortion and the birth of babies of low weight is significantly raised in celiac women, but is corrected by treatment with a GFD (60). Given the high frequency of CD in the general population, serological screening of pregnant women during the first trimester is considered appropriate, even though those women diagnosed with CD might run the risk of the aforementioned complications (61).

Other problems, such as impotence, sterility, or loss of sexual appetite, are also frequent in untreated patients (62).

Neurological affection

Various neurological diseases have customarily been associated with CD. A study by Hadjivassiliou et al. (63) showed that up to 57% of patients with neurological diseases of unknown cause (ataxias, peripheral neuropathies, myelopathies, myopathies, motor neuropathies and multiple mononeuritis) exhibit raised levels of anti-gliadin antibodies, the prevalence of CD in each group being greater than 16%.

CD may be associated with up to 8% of cases with neurological symptoms, basically those pertaining to cerebellar ataxia, epilepsy, peripheral neuropathy and multiple sclerosis. Patients with CD and neurological manifestations exhibit little digestive symptomatology, with the consequence that the gluten sensitivity is generally diagnosed late (64). The recognition of CD is important, given that the early suppression of gluten, after the onset of the

neurological symptoms, may lead to its improvement or even its complete disappearance. The pathogeny of the neurological involvement in CD is not well understood, but has been ascribed an autoimmune origin. In celiac patients with neurological symptoms the presence of anti-Purkinje cell and anti-SNC neuron antibodies has been shown (65).

Cerebellar ataxia is the neurological process that has most commonly been associated with CD, although other neurological forms of presentation of CD, such as epilepsy, myoclonus, etc., have been reported.

Other neuropsychiatric symptoms associated with CD, such as changes of character, irritability and depression, usually improve significantly once the disease has been diagnosed and treated with a GFD.

Liver diseases :

CD is often associated with changes in the liver. These occur in up to 10% of cases, generally presenting as a nonspecific reactive hepatitis. Analytical changes and histological lesions both disappear following gluten withdrawal. In these cases, it is not considered appropriate to carry out a liver biopsy, the technique only being applied when transaminase levels are not normalized after a long period on a GFD, or when a specific liver disease is suspected (66).

CD is a cause of persistent cryptogenic hypertransaminasemia and should be included in the determination of anti-tTG antibodies in the diagnostic protocols of these patients (67). It is thought that reactive hepatitis provoked in these patients is due to the increase in intestinal permeability, which provokes the passage of liver antigens through the portal venous system, producing a wide variety of autoimmune hepatic lesions (68).

The possibility that serious types of hepatopathy may occur has recently been raised, including in the form of acute, fulminant hepatitis, which it has been possible to control effectively by establishing a GFD, thereby avoiding the need for a liver transplant to treat this serious illness (69).

Hematological changes

The determination of hematological parameters can reveal evidence of such conditions as hyposplenism (thrombocytosis, stippled erythrocytes and Howell-Jolly bodies) or hypersplenism (leucopenia, thrombopenia), prothrombin deficiency, hypertransaminasemia, amongst others. However, ferropenic anemia is the most commonly found disorder.

Ferropenic anemia

Ferropenia and ferropenic anemia are the analytical and hematological changes most frequently associated with CD. They are caused by a deficiency in the intestinal absorption of iron (70). From a clinical perspective it is important to bear in mind that approximately 5% of patients with ferropenic anemia have CD arising from the same cause. Nutritional deficiencies alone do not explain this, and it appears that the inflammation contributes to its presence in some individuals (71). The percentage is even higher if we consider only refractory anemia.

In the case of ferropenic anemia of unclear origin, especially for patients who do not respond well to substitutive treatment by the oral administration of iron, an endoscopy must be carried out, including a duodenal biopsy, to rule out the presence of an associated CD (72).

Without doubt, the presence of the aforementioned associated diseases facilitates the diagnosis of celiac disease. Its treatment with a gluten-free diet improves its evolution and, in many patients, helps cure the disease.

Table 1. Risk Groups and Associated Diseases

- **First-degree relatives**
- **Down's and Turner's syndromes**
- **IgA selective deficiency**
- **Endocrine diseases**

Type 1 diabetes mellitus
Autoimmune thyroid diseases
Alopecia areata

- **Neurological diseases**

Cerebellar ataxia
Epilepsy
Peripheral neuropathy
Multiple sclerosis

- **Liver diseases**

Primary biliary cirrhosis
Autoimmune hepatitis
Autoimmune cholangitis
Idiopathic hypertransaminasemia

- **Rheumatological diseases**

Rheumatoid arthritis
Sjögren's syndrome

- **Heart diseases**

Idiopathic dilated cardiomyopathy
Autoimmune myocarditis

- **Cutaneous diseases**

Dermatitis herpetiformis
Psoriasis
Vitiligo

- **Others**

Iron-deficiency anemia
Osteoporosis
Increased risk of fractures
Infertility
Amenorrhoea
Dental enamel defects
Depression and anxiety
Chronic asthenia

References

- Schuphan D. Current concepts of celiac disease pathogenesis. *Gastroenterology* 2000; 119:234-42.
- Sollid LM. Molecular basis of celiac disease. *Ann Rev Immunol* 2000; 18:53-81.
- Farrell RJ, Kelly CP. Celiac sprue. *N Engl J Med* 2002; 346:180-8.
- Van Berge-Henegouwen GP, Mulder CJ. Pioneer in the gluten free diet: Willen-Karel Dicke 1905-1962 over 50 years of gluten free diet. *Gut* 1993; 34:1473-5.
- Shan L, Molberg O, Parrot I, et al. Structural basis for gluten intolerance in celiac sprue. *Science* 2002; 297:2275-9.
- Fasano A, Catassi C. Current approaches to diagnosis and treatment of coeliac disease: An evolving spectrum. *Gastroenterology* 2001; 120:636-51.
- Butterworth JR, Iqbal TH, Cooper BT. Coeliac disease in South Asian residents in Britain: comparison with white Caucasian coeliac patients. *Eur J Gastro Hepatol* 2005; 17:541-5.
- Riestra S, D. Fuentes D, Fernández E, Rodrigo L. Aspectos actuales de la enfermedad celíaca. *Rev Gastroenterol* 2001; 3:153-68.
- Riestra S, Fernández E, Bousño C, Rodrigo L. Enfermedad celíaca del adulto. *Gastroenterol Hepatol* 2001; 24:515.
- Riestra S, Fernández E, Rodrigo L, García S, Ocio G. Prevalence of coeliac disease in the general population of Northern Spain. Strategies of serological screening. *Scand J Gastroenterol* 2000; 35:409-12.
- West J, Logan RF, Hill PG, et al. Seroprevalence, correlates, and characteristics of undetected coeliac disease in England. *Gut* 2003; 52:960-5.
- Bingley PJ, Williams AJ, Norcross AJ, et al. Undiagnosed coeliac disease at age seven: population based prospective birth cohort study. *BMJ* 2004; 328:322-3.
- Gomez JC, Selvaggio GS, Viola M, et al. Prevalence of celiac disease in Argentina: screening of an adult population in the La Plata area. *Am J Gastroenterol* 2001; 96:2700-4.
- Murray JA, Van Dyck C, Plavak MF, Dierkising RA, Zinsmeister AR, Melton LJ. Trends in the identification and clinical features of celiac disease in a North American community 1950-2001. *Clin Gastroenterol Hepatol* 2003; 1:19-22.
- Gandolfi L, Pratesi J, Córdoba JCM, Tauil PL, Gasparin M, Catassi C. Prevalence of celiac disease among blood donors in Brazil. *Am J Gastroenterol* 2000; 95:689-92.
- Mäki M, Mustalahti K, Kokkonen J, Kulmala P, Haapalathi M, Kattunen T, et al. Prevalence of celiac disease among children in Finland. *N Engl J Med* 2003; 348:2517-24.
- Volta U, Bellentani S, Bianchi FB, et al. High prevalence of coeliac disease in the Italian general population. *Dig Dis Sci* 2001; 46:1500-5.
- Catassi C, Doloretta Macis M, Ratsch IM, et al. The distribution of DQ genes in the Saharawi population provides only a partial explanation for the high celiac disease prevalence. *Tissue Antigens* 2001; 58:402-6.
- Carlsson A, Agardh D, Borulf S, Grodzinsky E, Axlesson I, Ivarsson SA. Prevalence of celiac disease: before and after a national change in feeding recommendations. *Scand J Gastroenterol* 2006; 41:553-8.
- Thyssen TEH. Ten cases of idiopathic steatorrhea. *QJ Med.* 1935; 4:359-65.
- Greco L, Romino R, Coto I, Cosmo ND, Percopo S, Maglio M, et al. The first large population based twin study of coeliac disease. *Gut* 2002; 50:624-8.
- King AL, Ciclitira PJ. Celiac disease: Strongly heritable, oligogenic, but genetically complex. *Mol Genet Metab* 2000; 71:70-5.
- Neuhausen SL, Feolo M, Fernham J, Book L, Zone JJ. Linkage analysis of HLA and candidate genes for celiac disease in a North American family based study. *BMC Med Genetics* 2001; 2:12.
- Sollid LM, Lie BA. Celiac disease genetics: current concepts and practical applications. *Clin Gastroenterol Hepatol* 2005; 3:843-51.
- Bolognesi E, Karell K, Percopo S, et al. Additional factor in some HLA DR3/DQ2 haplotypes confers a fourfold increased genetic risk of celiac disease. *Tissue Antigens* 2003; 6:308-16.
- Johnson TC, Diamond B, Memeo L, et al. Relationship of HLA-DQ8 and severity of celiac disease: comparison of New York and Parisian cohorts. *Clin Gastroenterol Hepatol* 2004; 2:888-94.
- Abrams JA, Diamond B, Rotterdam H, Green PHR. Seronegative celiac disease increased prevalence with lesser degrees of villous atrophy *Dig Dis Sci* 2004; 49:546-50.
- Lin J, Jue SH, Holopainen P, Terwilliger J, Tong X, Gruun A et al. Genomewide linkage analysis of celiac disease in Finnish families *Am J Hum Genet* 2002; 70:51-9.
- López Vázquez A, Rodrigo L, Fuentes D, Riestra S, Bousño C, García-Fernández S, Martínez-Borra J, González S, López-Larrea C. MICA-A5.1 allele is associated with atypical forms of celiac disease in HLA-DQ2 negative patients. *Immunogenetics* 2002; 53:989-91.
- González S, Rodrigo L, López-Vázquez A, Fuentes D, Agudo-Ibáñez L, Rodríguez-Rodero S, Fernández-Morera JL, Martínez-Borra J, López-Larrea C. Association of MHC class I related gene B (MICB) to celiac disease. *Am J Gastroenterol* 2004; 99:676-80.
- Rueda B, Pascual M, López-Nevot MA, et al. Association of MICA-A5.1 allele with susceptibility to celiac disease in a family study. *Am J Gastroenterol* 2003; 98:359-62.
- Rodríguez-Rodero S, Rodrigo L, Fdez-Morera JL, Martínez-Borra J, López-Vázquez A, Fuentes D, López-Arbesú R, López-Soto A, González S, López-Larrea C. MHC class I chain-related gene B promoter polymorphisms and celiac disease. *Hum Immunol* 2006; 67:208-14.
- Maiuri L, Ciacci C, Ricciardelli I, et al. Association between innate response to gliadin and activation of pathogenic T cells in coeliac disease. *Lancet* 2003; 362:30-7.
- Solliger B, Abken H, Ferrone S. HLA-G and MIC expression in tumors and their role in anti-tumor immunity. *Trends Immunol* 2003; 24:82-7.
- Groh V, Rhinehart R, Rudolph-Habector J, et al. Co-stimulation of CD8 T cells by NKG2D via engagement by MIC induced on virus-infected cells. *Nat Immunol* 2001; 2:255-60.
- King AL, Moodie SJ, Fraser JS, Curtis D, Reid E, Dearlove AM, Ellis HH, Ciclitira PJ. CTLA-4/CD28 gene region is associated with genetic susceptibility to coeliac disease in UK families. *J Med Genet* 2002; 39:51-54.
- Raivio T, Kaukinen K, Nemes E, et al. Self transglutaminase-based rapid coeliac disease antibody detection by a lateral flow method. *Aliment Pharmacol Ther* 2006; 24:147-54.
- Kaukinen K, Partanen J, Mäki M, Collin P. HLA typing in the diagnosis of celiac disease. *Am J Gastroenterol* 2002; 97:695-9.
- Logan RFA. Problems and pitfalls in epidemiological studies of coeliac disease. In: Auricchio S, Visakorpi JK, eds. *Common food intolerance 1: Epidemiology of coeliac disease*. Basel Karger 1992; 14-24.
- Cronin CC, Shanahan F. Exploring the iceberg—the spectrum of celiac disease. *Am J Gastroenterol* 2003; 98:518-20.
- Bottero G, Cataldo F, Rotolo N, et al. The clinical pattern of subclinical silent celiac disease: An analysis on 1026 cases. *Am J Gastroenterol* 1999; 49:691-6.
- López-Vázquez A, Rodrigo L, Fuentes D, Riestra S, Bousño C, García-Fernández S, Martínez-Borra J, González S, López-Larrea C. MHC class I chain related gene A (MICA) modulates the development of coeliac disease in patients with the high risk heterodimer DQA1*0501/DQB1*0201. *Gut* 2002; 50:336-40.
- López-Vázquez A, Fuentes D, Rodrigo L, González S, Moreno M, Fernández E, Martínez-Borra J, López-Larrea C. MHC class I region plays a role in the development of diverse clinical forms of celiac disease in a Saharawi population. *Am J Gastroenterol* 2004; 99:662-7.
- D'Amico MA, Holmes J, Stavropoulos SN, et al. Presentation of pediatric celiac disease in the United States: prominent effect of breastfeeding. *Clin Pediatric* 2005; 44:249-58.
- Green PHR, Stavropoulos SN, Panagi SG, et al. Characteristics of adult celiac disease in the USA: Results of a national survey. *Am J Gastroenterol* 2001; 96:126-31.
- Rampertab SD, Pooran N, Brar P, Singh P, Green PH. Trends in the presentation of celiac disease. *Am J Med* 2006; 355:9-14.
- Dickey W, Kearney N. Overweight in celiac disease: prevalence, clinical characteristics and effect of a gluten-free diet. *Am J Gastroenterol* 2006; 101:2356-9.
- Green PH. The many faces of celiac disease: clinical presentation of celiac disease in the adult population. *Gastroenterology* 2005; 128:74-78.
- Bogenrieder T, Stolz W. From the new world. Louis A. Duhring and dermatitis herpetiformis. *Hautartz* 2003; 54:167-72.
- Pfeiffer C. Dermatitis herpetiformis. A clinical chameleon. *Hautartz* 2006; 57:1021-8.
- Beutner EH, Plunkett RW. Methods for diagnosis dermatitis herpetiformis. *J Am Acad Dermatol* 2006; 55:1112-3.
- Hervonen K, Karell K, Holopainen P, Collin P, Partanen J, Reunala T. Concordance of dermatitis herpetiformis and celiac disease in monozygous twins. *J Invest Dermatol* 2000; 115:990-3.
- Corazza GR, Andreani ML, Venturo N, Bernardi M, Tosti A, Gasbarrini G. Celiac disease and alopecia areata: report of a new association. *Gastroenterology* 1995; 109:1333-7.
- Bardella MT, Marino R, Barbareschi M, Bianchi F, Faglia G, Bianchi P. Alopecia areata and coeliac disease: no effect of a gluten-free diet on hair growth. *Dermatology* 2000;

- 200: 108-10.
- 55.- Collin P, Reunala T. Recognition and management of the cutaneous manifestations of celiac disease. A guide for dermatologists. *Am J Dermatol* 2003;4: 13-20.
- 56.- Michaelsson G, Gerden B, Hagforsen E, et al. Psoriasis patients with antibodies to gliadin can be improved by a gluten-free diet. *Br J Dermatol* 2000; 142:44-51.
- 57.- Lee SK, Green PH. Celiac sprue (the great modern-day imposter). *Curr Opin Rheumatol* 2006; 18: 101-7.
- 58.- Meyer D, Stavropoulos S, Diamond B, Shane E, Green PH. Osteoporosis in a North American adult population with celiac disease. *Am J Gastroenterol* 2001;96: 112-9.
- 59.- Hernández L, Green PH. Extraintestinal manifestations of celiac disease. *Curr Gastroenterol Rep* 2006;8:383-9.
- 60.- Martinelli P, Troncone R, Paparo F, Torre P, Trapanese E, Fasano C, Lamberti A, Budillon G, Mardone G, Greco L. Coeliac disease and unfavourable outcome of pregnancy. *Gut* 2000;46: 332-5.
- 61.- Ludvigsson JF, Montgomery SM, Ekblom A. Celiac disease and risk of adverse fetal outcome: a population-based cohort study. *Gastroenterology* 2005; 129:454-63.
- 62.- Ciacci C, d'Agate C, De Rosa A, Franzese C, Errichiello S, Gasperi V, Pardi A, Quagliata D, Visentini S, Greco L. Self-rated quality of life in celiac disease. *Dig Dis Sci.* 2003; 48: 2216-20.
- 63.- Hadjivassiliou M, Boscolos S, Davies-Jones GAB, Grünewald RA, Not T, Sanders DS, et al. The humoral response in the pathogenesis of gluten ataxia. *Neurology* 2002; 58: 1221-6.
- 64.- Volta V, De Giorgio R, Petrolini N, Stanyhellini V, Barbara G, Granito A, et al. Clinical findings and anti-neuronal antibodies in coeliac disease with neurological disorders. *Scand J Gastroenterol* 2002;37: 1276-81.
- 65.- González S, Rodrigo L, Salas-Puig J, Astudillo A, Fuentes D, López-Vázquez A, López-Larrea C. Progressive myoclonic ataxia associated with antibodies against Purkinje cells in a celiac patient. *Rev Esp Enferm Dig* 2005;97:918-21.
- 66.- Huguet JM, Ruiz L, Durá AB, Latorre M, Medina E. Hypertransaminasemia in adult celiac disease. *Gastroenterol Hepatol* 2007; 30:427-8.
- 67.- Riestra S, Fernández E, Rodrigo L. Afectación hepática en la enfermedad celiaca. *Rev Esp Enferm Dig* 1999;91:846-52.
- 68.- Bai D, Brar P, Holleran S, Ramakrishnan R, Green PH. Effect of gender on the manifestations of celiac disease: evidence for greater malabsorption in men. *Scand J Gastroenterol* 2005;40: 183-7.
- 69.- Kaukinen K, Halme L, Collin P, et al. Celiac disease in patients with severe liver disease: gluten-free diet may reverse hepatic failure. *Gastroenterology* 2002; 122:881-8.
- 70.- Harper JW, Holleran SF, Ramakrishnan R, Bhagat G, Green PH. Anemia in celiac disease is multifactorial in etiology. *Am J Hematol* 2007; 82:996-1000.
- 71.- Sari R, Yildirim B, Serinc A, Buyukberber S. Gluten-free diet improves iron-deficiency anaemia in patients with celiac disease. *J Health Popul Nutr* 2000;18: 54-6.
- 72.- Riestra S, Domínguez F, Fernández-Ruiz E, García-Riesco E, Nieto R, Fernández E, Rodrigo L. Usefulness of duodenal biopsy during routine upper gastrointestinal endoscopy for diagnosis of celiac disease. *World J Gastroenterol* 2006; 12:5028-32.