Chapter 1

Celiac Disease and Non-Celiac Gluten Sensitivity

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Doi: http://dx.doi.org/10.3926/oms.236

How to cite this chapter

Peña AS, Rodrigo L. *Celiac Disease and Non-Celiac Gluten Sensitivity.* In Rodrigo L and Peña AS, editors. *Celiac Disease and Non-Celiac Gluten Sensitivity.* Barcelona, Spain: OmniaScience; 2014. p. 25-44.

Abstract

This chapter explains the title of this volume and it highlights the importance of recognizing non-celiac gluten sensitivity. It briefly discusses the topics covered in all the chapters within the context of a new definition as well as recent developments in China, Mexico, El Salvador and Costa Rica. The immunological differences between celiac disease and non-celiac gluten sensitivity are reviewed as well as the clinical and pathological definition and the differences between celiac disease, gluten allergy, gluten sensitivity and non-celiac gluten intolerance.

The physiological and immunological effects that can be triggered by wheat products are also briefly summarized without mentioning somatization disorders that may apply to some patients with sensitivity or food intolerance. New concepts about placebo and nocebo are described. This new insight suggests the need to include protocols similar to those that can be applied to diets that include or exclude gluten. It is clear that the two opposing mechanisms of placebo and nocebo may come into play not only when administering drugs but also when specific diets are used as treatment. Subsequently, attention is drawn to the chapters on diagnostic techniques such as celiac disease serology, endoscopy and histopathology, as well as those that deal with the various clinical forms of CD in children and adults. Finally, there is a description of the topics relating to celiac disease on which the authors have expertise.

1. Introduction

This chapter sets out a great deal of the history of celiac disease from where Professor García Nieto leaves off in **chapter 2**: "History of celiac disease", that is to say, after Dicke's[1] discovery of the value of a gluten-free diet and the first description of morphological alterations of the proximal small intestine obtained in surgical resections by Paulley[2] as well as in Margot Shiner's[3,4] peroral biopsies. The chapters that follow explore the situation of celiac disease in countries like China and Costa Rica (**chapters 3 and 10**), El Salvador and Mexico (**chapters 4 and 5**, respectively). Knowledge in these countries is skimpy, but quite interesting since it pertains to very heterogeneous populations where celiac disease was thought to be inexistent. **Chapter 5** raises the possibility that other cereals, including maize, could affect some celiac patients. This last item is yet to be confirmed since it still must be rigorously proven that this is not due to cross contamination. These authors from Mexico argue that oats and maize, which belong to the same subfamily and family of gramineae as wheat[5] could stimulate an immune response. They also confirm that bovine milk caseins may exacerbate celiac disease. Previously, it had been observed that bovine caseins induce an inflammatory reaction in a contact test in the rectal mucosa of celiac patients.[6]

2. Non-Celiac Gluten Sensitivity (NCGS)

Before proceeding with a short description of this book, its title will be justified and the importance of recognizing non-celiac gluten sensitivity will be highlighted even though, for the time being, this syndrome is not fully understood.

This issue may have been the one with the greatest impact during the last decades, specially over the internet, in patients' associations and in the food industry. As discussed below, there is a lack of systematic studies which could enable an understanding and definition of this syndrome and, especially, an understanding of its possible impact on public health services. In this we fully agree with the view expressed by Corazza and his group, who emphasize the lack of a clear definition of non-celiac gluten sensitivity. This obstacle is of, course fundamentally related to the cause of this variegated disease, whose symptoms are presumably caused by different mechanisms.[7-10]

It is therefore unsurprising that, recently Dr. Spence of Glasgow, Scotland wrote: "Do you think non-celiac gluten sensitivity exists?" According to a recent poll undertaken by the general practitioners' magazine in England, the *British Journal of Medicine,* 66% of the 941 who were polled and who have had access to higher education, said they believe it does exist, despite lack of scientific evidence. Besides, about 20 % of the American population purchase gluten-free products and, by 2017, it is estimated that this market will be worth about 6.6 million dollars.[11]

The term *non-celiac gluten sensitivity* was first used in 1978, by Ellis and Linaker,[12,13] even though a few months before Hemmings[14] had reported two patients with satisfactory response to a gluten-free diet. In both cases, as in others later on, in Israel and England, those patients suffered from allergy to dietary wheat.[15,16] These isolated cases preceded the first double-blind study performed in six non-celiac patients who clearly showed the deleterious effects the ingestion of 20g of gluten per day.[17] Since then, a few randomized, placebo-controlled studies have shown that is increasingly clear that these patients suffer from non-celiac gluten sensitivity with

heterogeneous etiology. Table 1 summarizes the systematic studies that have been published in medical literature until now. These are studies cannot be compared to each other since their patient selection is not uniform; besides, the protocols followed to establish the effects of gluten in each case are different. The first study group in Birmingham included seventeen patients with chronic diarrhea, of which nine responded to a GFD. Intestinal biopsy specimens revealed increased intraepithelial lymphocytes and plasma cells, not as high as in celiac patients, but returning to normal with a GFD. Three were HLA-B8+ (probably HLA-DQ2+). Several years later, the Peter R. Gibson's group[18] from Australian conducted a double-blind provocation, randomized, placebo-controlled trial in patients with irritable bowel syndrome, in which celiac disease was excluded; it was observed that participants who ingested gluten did not experience symptom improvement in their symptoms (13 of 19 patients) against those who received placebo, 6 of 15 (40%) while both groups followed a gluten-free diet. However, recently, the same Australian group,[19] in a double-blind crossover study of 37 subjects with non-celiac gluten sensitivity and irritable bowel syndrome, found no evidence of specific or dose-dependent gluten effects when patients consumed a diet low in FODMAPs (Fermentable Oligo-saccharides, Disaccharides, Mono-saccharides and Polyols). Even when given a high-gluten content diet (16g gluten/day) or a diet with low-gluten content (2g gluten/day supplemented with 14g whey protein) the patients had no more symptoms than with a control diet based on 6g whey protein per day for 1 week.

Ref.	Patients	Symptoms	Overload	Placebo or GFD
17	17 - patients with non-celiac chronic diarrhea	Diarrhea with positive response to GFD (9 females)	20 g. gluten/day Positive	Gluten-free flour
18	34 - Irritable Colon Syndrome Non-celiacs	Intestinal symptoms	16 g. gluten/day Positive	Gluten-free bread
20-22	276 - Irritable Colon Syndrome Non-celiacs	Intestinal symptoms 70 sensitivity only to wheat 206 sensitivity to several types of food	13 g. gluten capsules/day Positive	Xylose capsules
23-25	45 - Irritable colon Syndrome Non-celiacs	Diarrhea (Roma II)	22 NGFD (11 HLA-Q2/8 +) Altered intestinal barrier in HLA-DQ2/8+ patients	23 GFD (12 HLA-Q2/8 +)
19	59 - Irritable colon Syndrome Non-celiacs	Diarrhea (Roma III)	GFD, with FODMAP 16g gluten/day; 2g gluten/day 37 patients 7 days; 22 patients. 3 days Negative	GFD, without FODMAP 16g whey/day

GFD= gluten-free diet; NGFD= non-gluten-free diet; Ref.= Reference; FODMAP=Fermentable Oligo-saccharides, Disaccharides, Mono-saccharides and Polyols)

Table 1. Systematic randomized studies of patients with non-celiac gluten sensitivity.

Two different studies of patients with irritable bowel syndrome in whom celiac disease had been previously excluded (Table 1) have been published recently. In a study undertaken by Carroccio et

al[20-22] wheat sensitivity also affected patients who do not have celiac disease and lack the specific HLA-DQ antigens associated with the disease. In these patients an increase of eosinophils and basophil activation in the lamina propria of the duodenum and colon were found. Therefore, in gluten sensitivity, wheat had multiple functions more consistent with food allergy. In a more recent study by Vazquez-Roque et al[25] it was shown that a diet containing gluten produces a reversible alteration of the intestinal barrier in patients with irritable bowel syndrome and diarrhea in those patients who carry HLA-DQ2/8.

Many of the described observations have helped to define non-celiac gluten sensitivity as a reaction to gluten in which allergic and autoimmune mechanisms are excluded. That is to say, anti-EMA and/or anti-tTG patients test are usually negative although antigliadin antibodies may be present; but their duodenal mucosa is normal. Symptoms disappear with a GFD and reappear with gluten overload. As Sapone et al. have written, so far, this is essentially an exclusion diagnosis.[26] his implies that this is an entity distinct from celiac disease although there is sufficient evidence that it is a syndrome since the alterations described in patients from Italy are not seen in similar patients in USA or Australia as it can be appreciated with immunological studies. In Germany it has been found that patients who have irritable bowel syndrome with a predominance of diarrhea with gliadin IgG antibodies and HLA-DQ2, but who have normal biopsies, usually respond to a GFD.[27, 28] These patients may be potentially celiac, since simple morphological studies may not be sensitive enough to exclude an immunological response. There patients are probably part of the heterogeneity of celiac disease. This does not apply to Carroccio's onservations[20, 21] since in their study wheat sensitivity also affected patients without HLA-DQ2 or HLA-DQ8 markers.

3. Immunological Differences between Celiac Disease and Non-Celiac Gluten Sensitivity

In many of Carroccio's[20, 21] patients, an increase of eosinophils in the duodenal and colon lamina propria was found, suggesting that basophil activation may be a useful marker for wheat sensitivity. In another group of non-celiac gluten sensitive patients, there was no increase in the expression of the IL-17 cytokine in comparison with a group of celiac patients who did show an increase of this same cytokine in the intestinal mucosa.[26, 29, 30] Subsequent studies by the same group have shown that non-celiac gluten sensitivity is not associated with an increased intestinal permeability and that, in these cases, the expression of T FOXP3 regulatory cell markers is decreased. Conversely, in these patients there is a significant increase in the expression of claudin 4 and of the innate immunity marker, the Toll-like receptor 2.[30] These studies suggest that the difference between these two groups is that, in celiac disease, both the innate and the acquired immunity are increased, whereas in gluten sensitivity patients only the innate immunity is activated by gluten. Recent Norwegian studies indicate that the immune response is more complicated and that more studies are needed to understand the symptoms. In one recent study, thirty HLA-DQ2+ celiac and fifteen with non-celiac gluten sensitivity patients were studied before and after a gluten-free diet , feeding them four slices of gluten-containing bread for three days. Duodenal biopsies were collected before and after exposure. In celiac patients the tumor necrosis factor alpha and interleukin-8 were increased after *in vivo* gluten challenge. The gamma

interferon level in treated celiac patients was increased both before and after exposure to gluten and did not increase significantly. IFN-alpha was also found to be activated upon stimulation with gluten. By contrast, in patients with non-celiac gluten sensitivity, only IFN-gamma was significantly increased. The number of intra-epithelial lymphocytes CD3+ T was higher in patients compared with controls independently of gluten overload, although they were lower in the latter than in the former and there was an increase of IFN-gamma after gluten challenge.[31]

4. Celiac Disease: New Definitions

In the past 10 years it has become clear that, along with celiac disease, there are other conditions related to gluten consumption. a) Wheat allergy (the less common) b) Autoimmune disease, celiac disease, dermatitis herpetiformis and gluten ataxia, c) Sensitivity to gluten, which is possibly immune-mediated and now the most common.[26] and d) Gluten intolerance. Table 2 shows a classification system comprising four main types.

Celiac Disease	Allergy	Sensitivity	Intolerance
Intestinal and extraintestinal symptoms for days, weeks or years after ingesting gluten.	Intestinal and extraintestinal symptoms for minutes or hours after ingesting gluten.	Intestinal and extraintestinal symptoms for hours or days after ingesting gluten.	Intestinal and extraintestinal symptoms for hours or days after ingesting gluten.
No direct correlation with the amount, but enteropathy is still present. Reversibility feasible, but the mechanisms are unknown.	Small amounts provoke symptoms. Eosinophils in lamina propria. Wheat Anaphylaxis Desensitization is theoretically possible.	Variable response to different gluten amounts. Increased intraepitelial lymphocytes. Increased basophils in lamina propria.	The amount of gluten grams determines intensity and can be reversed. No enteropathy of any type.
Anti-Endomysium, anti-tTG, deamidated anti-gluten +.	Anti-IgE to wheat components including omega-5 gliadin and barley gamma3 hordein.	Anti-IgG-AGA+	Negative antibodies
HLA-DQ2 y/o HLA-DQ8	Unknown	No association	No association
Innate and acquired immunity activated	Allergy Anaphylaxis	Innate immunity	No immunological mechanisms
Associated and autoimmune diseases common.	Allergic diseases	Sensitivity to other kinds of food common.	Unknown.

Table 2. Clinical and pathophysiological differences between celiac disease, gluten allergy, non-celiac gluten sensitivity and gluten intolerance.

This classification does not include autoimmune enteropathy of unknown etiology. It is a fortunately rare and heterogeneous clinical condition, and few cases are described in adults.[32] It

is characterized by malabsorption along with the presence of antibodies which react against intestinal epithelial cells; as opposed to celiac disease, the histopathology of the duodenal mucosa is characterized by hyperplastic crypts and villous atrophy, accompanied by lymphocytosis in deep crypts, an increase in the number of apoptotic bodies and very few intraepithelial lymphocytes. Most children described have associated autoimmune diseases.[33-35]

This proposed classification differs from the definitions recently accepted at Oslo Consensus meeting.[36] Celiac disease is defined as a genetically predisposed autoimmune enteropathy caused by the ingestion of some peptides derived from wheat (gliadins and glutenins), barley (hordeins), rye (secalins), oats (avenines) and hybrids of these grains, such as kalmut and triticale (**chapters 21 and 23**). These cereals contain epitopes for which deamidation is important for binding to HLA -DQ2 and/or HLA-DQ8 molecules and recognition of T cells contributing to produce the spectrum of the characteristic changes of the duodenal and jejunal mucosa. These changes lead to production of intestinal symptoms and autoimmune reactions that may affect extraintestinal organs. The immune response can remain inactive until unknown environmental elements trigger the disease and, as opposed to what was thought to be a lifelong disease, it may be transitory.[37-39]

Strict adherence to a gluten-free diet (GFD) leads, in a few months, to a rapid and complete recovery of small intestinal mucosa architecture and function, as well as to a remission of symptoms and normalization of serological tests.

In the second place, in Oslo it was recommended that the term “gluten-related disorders” be used as a general term for all diseases triggered by gluten and it was suggested that the term “gluten intolerance” should not be used.[36]

Peptides capable of stimulating T cells T	**Components capable of stimulating dendritic cells**	**Alpha-amylase and trypsin Inhibitors**	**Opioid effect**	**Allergy and anaphylaxis**	**Placebo nocebo**
Acquired immunity response	Innate immunity response	Increased IL-8 and TNF-alpha, through TLR4-MD2-CD14 stimulation	Increased intestinal transit	Intestinal and extraintestinal symptoms	
Gluten epitopes recognized by T-cells restricted by HLA-DQ molecules	Increase in Claudin		Response to Naloxone	Antibodies in response to Omega-5 gliadin	
40	30	41	7,8, 42-44	45,46,47	19

Table 3. Several components of wheat and related cereals with immunological and physiological effects.

5. A New View of Placebo and Nocebo

There are few observations on placebo/nocebo regarding GFD[19] but is appropriate to briefly review recent concepts about these mechanisms which doctors (due to their interest in patient response to GFD) as well as patients who respond to this diet ought to take into account. Until recently, the well-known therapeutic effect of placebo was based primarily on the fact that the patient did not know that what he was taking was an inert substance and that, without suggestion, the placebo's magic disappears. There is, however, evidence that the use of placebos as analgesics not only help alleviate pain, but also that they do so through the same humoral mechanisms and neuroendocrine pathways that many drugs use. It is therefore not surprising that placebos work even when patients know they are placebos.

It has been shown recently in patients who have irritable bowel syndrome the possibility of studying the placebo effect even when they know that the drug is an inert substance: "placebo without deception".[48,49] Patients taking placebos showed a far superior improvement of their condition than that of those who did not receive this treatment. In this study, 80 patients (70% female) randomized for a three-week treatment period, were divided into two branches in order to compare those who received no treatment compared to those who took a placebo. The latter were informed that what was being given to them was an inert substance (the bottle of pills was even labeled "placebo") but they were told that there was evidence that it had beneficial effects.

Therefore, placebos work even if the patient knows they are inert substances. This opens an interesting field in therapy and it makes the ethical issue of deceiving the patient disappear, since the fact that he or she is being given a placebo is not being hidden from the patient. From now on, conscious attempts to identify and exploit the characteristics of medical visits in order to increase the placebo's effects are an ethical way to use what is known about its mechanisms, to improve the clinical outcomes.

Regarding the nocebo effect, it generates negative expectations in the patient and, it exemplifies the old saying "fear makes you sick", it also explains why an analysis of placebo-controlled trials shows that almost 25% of patients taking placebo reported side effects that should not exist. Although there is less research on nocebo effects and therefore less documentation, the results of the studies are consistent with the fact that the placebo and nocebo effects are real. If, as argued before, a placebo can help the healing process or alleviate pain, a nocebo has the opposite effect – it makes patients feel worse. This is partly so because nocebo studies have been limited due to ethical restrictions, since a nocebo procedure is stressful and leads to anxiety. One theory that tries to explain the nocebo effect argues that just as placebo activates brain endorphins to relieve pain, nocebo activates other receptors that stimulate the production of hormones or other pathways that affect pain perception. In support of this view, it should be noted that drugs used to treat anxiety can mitigate the pain of the nocebo effect. Perhaps the chemical imbalances that contribute to anxiety can also be the basis of the nocebo response. The latest scientific evidence supports this theory; the placebo and nocebo effects arise from brain processes that triggered by psychological mechanisms such as expectation and conditioning.

Experimental tests have shown that negative verbal suggestions induce anticipatory anxiety about an impending increase in pain levels, this triggers the activation of the cholecystokinin which, in turn, facilitates pain transmission. It has been found that antagonists of this hormone block anxiety-induced hyperalgesia. These observations open up the possibility of new therapeutic strategies when pain has an important anxiety component.[50-53]

Psychological factors such as anxiety, depression and hypochondria increase the nocebo effect. Previous negative experiences and the words used to describe medical side effects may also increase the nocebo effect.

This new insight suggests the need to incorporate similar protocols to the effects that a gluten-free or non gluten-free diet may have. It is clear that these two opposing mechanisms, placebo and nocebo, are involved. Expectations can bias sensory evidence and therefore the patient and the physician must obtain an appropriate balance will result in the updating of expectations of a procedure, a drug or a product involved in the prescribed diet. The following chapters discuss relevant aspects of current understanding of celiac disease.

6. Genetics

As reviewed in the chapter by Dr. Bilbao's group (**chapter 6**), celiac disease has a genetic predisposition. Linkage in families and association studies have largely confirmed the importance of HLA-DQ although these genes account for approximately 50 % of inherited traits. Genome-wide association studies (GWAS) which analyzed thousands of single nucleotide polymorphisms (SNPs) have shown that celiac disease is not an exception among other autoimmune diseases in which multiple genes from different chromosomes contribute to modulating the immune response to gluten. However, epidemiological studies have shown that certain environmental factors also are important in the expression of the disease. In adults, a study from the Mayo Clinic in Rochester, Olmsted County , Minnesota, USA[54] found that between 2000 and 2010, the number of new cases of celiac disease has increased from 11 per 100,000 to 17 people 100,000. 63% of the new cases were women and specially until 2004. It is possible that this increased incidence of celiac disease may be due in part to improved diagnosis, as well as to a better understanding of the symptoms and signs of celiac disease along with knowledge of risk groups and changes in the environment, changes in diet and high consumption of foods containing gluten, use and abuse of antibiotics and infections. In Sweden, in two cohorts of children with different infant feeding, it was found that those born in 1997 (22 per 1000) have a significantly lower risk of developing celiac disease compared with those born in 1993 (29 per 1000). The 1997 cohort had a higher proportion of infants in which gluten was introduced into the diet in small amounts while still being breastfed.[55] Recent studies have clearly shown that neither breast feeding or the late introduction of gluten[56] nor introducing gluten to infants at 4 to 6 months of age 57 modified the risk for celiac disease in infants who had a first-degree relative with celiac disease. Since high-risk HLA–DQ genotypes are an important predictor of disease in these children[56, 57] further studies aimed at identifying environmental factors are important to understand the different prevalence of celiac disease.[42]

7. Immunology

Immunological theory explains the changes observed in the lamina propria of the intestinal mucosa invoking a response involving CD4+ T cells, HLA-DQ2/8 restricted and IFN- gamma release. However, innate immunity acts on the intraepithelial compartment and also contributes to this increase with a direct toxic effect of gluten on the epithelium (**chapter 7**).

Gluten-derived peptides, the insoluble protein fraction of wheat, barley or rye trigger an immune response in susceptible individuals. Some gluten peptides are relatively undigestible by human proteases. The 33-mer peptide, the 17-mer, and other gliadin oligopeptides contain epitopes that are toxic when deamidated by tissue transglutaminase. These may be presented to the immune system by HLA-DQ2/DQ8 molecules and induce a proinflammatory cytokines response, resulting in epithelial damage.

There are other additional peptide sequences which initiate innate immune cytotoxic responses in the epithelium and increase the intestinal permeability through the expression of zonulin which facilitates the passage of large peptide fragments to the lamina propria.[58-60]

8. Diagnostic Techniques in Celiac Disease

Chapter 8 describes the usefulness of several serological tests in screening, diagnosis and monitoring of patients with celiac disease. **Chapter 9** discusses the value of endoscopy and **chapter 10** discusses the difficulties and value of histopathological diagnosis. The advances in the sensitivity and specificity of serological tests and the difficult in assessing the histopathology of celiac disease are changing the view that the morphological spectrum of the intestinal biopsy specimens is not always the gold standard and particularly in children when the specific antibody titers are highly elevated the diagnosis can be reached without performing the biopsies.[61]

9. Clinical Presentation of Celiac Disease

Chapters 11 and 12 describe the variety and richness of this disease in children and adults. Both discuss new guidelines to facilitate diagnosis, risk groups and treatment, including emerging treatments.

Chapter 13 gives a thorough answer to such an important question in clinical practice as: When Marsh 1 type lesions can be considered indication of celiac disease? This histological finding is not produced exclusively by gluten, however, at present is thought to constitute one of the most common forms of presentation in adult celiac patients. Different anatomical and pathological classifications of celiac disease is discussed, along with its various application criteria and differential diagnoses in relation to other processes. A relevant issue to this kind of manifestation is that, despite having negative celiac serology in over 80% of the cases, the severity of the clinical symptoms can be very similar to the forms of celiac disease with clear villous atrophy.[62,63]

Chapter 14 reviews the diverse extra-intestinal manifestations of celiac disease. Some diseases are caused by chronic disorders associated with defects in intestinal absorption, others share the same genetic basis and some are rare. Celiac disease has been proposed as a model to understand the role of MHC class II molecules in human immunopathology, to analyze the mechanisms that link tolerance to food proteins and autoimmunity.[64,65] The importance of detection lies not only in its confirmation, but patients also benefit from dietary treatment since after the exclusion of gluten from the diet, some patients experience partial benefits while others experience a complete clinical remission. In a retrospective study of 924 celiac patients from 27 adult and pediatric centers in France it was found that those who were at greater risk of developing autoimmune diseases are those who were diagnosed early in life and who have a family history of autoimmune problems. The gluten-free diet has a clear protective effect.[66]

Chapter 15 tackles the interesting relationship between celiac disease and bone metabolism disorders, both in children and adults. There is high prevalence of osteoporosis and an increased risk of fractures, in all stages of life for CD patients, increasing after menopause and upon reaching an advanced age. It is advisable to attempt an early detection of these disorders, mainly osteoporosis by performing serial studies of metabolic bone density periodically. Its prevalence increases with the presence of atrophied villi.[67] The gluten-free diet improves the intestinal calcium absorption, but cases with advanced osteoporosis need not only supplementary calcium, but also vitamin D supplements and bisphosphonate intake.

Chapter 16 deals with the relationship between the so-called functional gastrointestinal disorders which are very common in clinical practice, and their possible relationship to celiac disease. Thus, patients diagnosed with a functional digestive disorder, such as functional dyspepsia and/or irritable bowel syndrome, may be misdiagnosed and actually have celiac disease. This happens more often if clinical diagnostic studies are not completed with celiac serology, genetic markers and duodenal biopsies. Many of them have Type-1 Marsh lymphocytic enteritis and clearly respond to a gluten-free diet. This consideration has important implications not only in terms of morbidity and mortality resulting from delayed diagnosis of celiac disease, but also leads to a prolonged decline in their quality of life which may be recovered following a gluten-free diet and also saving money by avoiding unnecessary pharmacological treatment.[68-71] The relationship between IBS and non-celiac gluten sensitivity has been amply discussed earlier in this chapter and in the recent medical literature including the role of FODMAPs in controlling the symptoms.[19,22,72]

Chapter 17 discusses the major intestinal complications of CD, such as refractoriness which fortunately is rare, since it occurs in fewer than 5% of celiac patients. There are two types of refractory celiac disease. Type I is less serious and can be treated more effectively with immunomodulators and therefore, has a better prognosis. Type 2, is more severe, it may lead to the development of intestinal T-cell lymphoma, which of course carries a worse prognosis. There is no consensus on the most effective treatment for this serious complication. For the differential diagnosis of both forms require immunophenotyping of intraepithelial lymphocyte populations by duodenal biopsies and studies of their characteristics using flow cytometry. Other possible causes of lack of response to GFD must be ruled out first.[73,74]

Chapter 18 discusses medical follow-up of celiac patients, which cannot be performed according to strict rules since there is no consensus about this subject. It describes the four most commonly used procedures: regular clinical follow-up, annual measurement of specific

antibodies to celiac disease, regular duodenal biopsies (no clearly defined in time periods) and control of adherence to the GFD through structured questionnaires. All of these approaches are useful and necessary, as well as the detection and prevention of nutritional deficiencies and the periodical screening for the presence of associated diseases.[36,75,76]

Chapter 19 discusses the issue of quality of life and psychological distress in celiac patients. Undoubtedly the majority of patients with celiac disease have a marked worsening of their quality of life when diagnosed, secondary to multiple digestive and associated diseases that they have, together with the long diagnostic delay characteristic in most cases. This situation improves significantly with strict adherence to a gluten-free diet until a complete normalization is achieved.[77] Anxiety disorders are common at diagnosis and they are considered to be reactive forms due to lack of knowledge at the beginning or to difficulties in adhering to the diet. Depressive disorders have also negative effects and should be identified and, if necessary, treated properly, especially at the beginning of the GFD.[78-80] Recent studies at the Columbia University in New York indicate the frequent presence of chronic headaches in these patients and they found that up to 30% of their celiac patients, 56% of non-celiac gluten sensitivity, 23% in patients with inflammatory bowel disease and 14% of healthy controls. There was also a higher prevalence of migraine in these three groups of patients, being the female gender, depression and anxiety, the independent factors for migraine.[81]

Chapter 20 reviews the experiences of a large group of celiac patients, along with the results of various surveys on the acceptability of GFD, cultural aspects that influence adherence to GFD and the impact of a CD diagnosis, both personally and as a member of a family. It is a very interesting study which highlights the importance of the physician's attitude when diagnosing and explaining to the patient the disease characteristics as well as the cultural, personal and family variables determining compliance to GFD or the existence of various transgressions or even quitting GFD.[82-84] Recently in Norway, a comparative study was undertaken comparing 22 patients with celiac disease versus 31 patients with non-celiac gluten sensitivity during an overload of gluten for 3 days. A comparison group of 40 healthy controls was included. There were no significant differences between patients regarding personality traits, somatization level, quality of life, anxiety and depressive symptoms. Somatization was low in both groups. Patients with non-celiac gluten sensitivity had more symptoms than patients with celiac disease after exposure to gluten.[85]

Chapter 21 addresses the issue of detecting the immunotoxic gluten fractions in order to find applications in the food safety area. These researchers observed that there is a wide range of variability in the immunotoxic potential of different varieties of cereals, particularly barley and oats. They have shown that there is a strict correlation between the amount of gluten and immunotoxic potential due to the fact that some gluten epitopes may be less immunogenic than others and therefore require a higher concentration to cause an equivalent toxic effect. There are currently available specific monoclonal antibodies against various toxic gluten fractions, one of the most used methods in food analysis; these are very sensitive and specific and are determined by Elisa techniques. The authors study the toxic potential of oats, about which there is much discussion in the literature discussing whether they can be allowed as part of the GFD.[86, 87] They have analyzed three varieties of oats and found great variability in their gluten content, with different toxicity; this opens the future possibility to include the less toxic oats fractions in certain kinds of foods. A similar phenomenon occurs with several varieties of barley, demonstrating that the wild varieties are more toxic than the domestic ones. All this opens up

exciting new possibilities for expanding a gluten-free diet, with the possible addition of oat flour and barley poor in toxic peptides and therefore well tolerated by celiac patients.[88,89]

Chapter 22 provides valuable information on the technological, nutritional and sensory characteristics of gluten-free cereal products and also discusses issues related to the design and development of these foods. Gluten-free diets can cause, in the long run, nutritional imbalances and due to specific nutrient deficiencies and it proposes the need to improve the nutritional composition of gluten-free food with the addition of nutrients such as omega-3 oils, specific proteins fiber, probiotics and prebiotics.[90-92] These recommendations are partially due to recent findings by Canadian researchers regarding the impact of long term gluten-free diets, highlighting the need for improved training and education of dietitians and other health care providers, as well as in workers in the gluten-free food industry, in order better help to the people for improving their adherence to a GFD and their quality of life.[93]

In **Chapter 23** contains clear and precise information regarding current possibilities of producing varieties of wheat gluten by the novel methods of silencing the genes involved in the generation of this peptide. This opens up numerous possibilities for future development of wheat flours which, prior to their modification and treatment, are practically free from gluten and therefore suitable for nutrition and treatment not only of celiac patients, but also for non-celiac gluten sensitives and people with anaphylactic reactions to the various components of wheat. In order to be marketed they will have to pass through numerous controls laid down by diverse national food agencies, as well as through the authorization of international health authorities, since they belong to the transgenic product category[94,95]

Chapter 24 discusses the issue of the relationship between intestinal microbiota and celiac disease. As it is well known, the intestinal flora of the colon is variegated and colonized by millions of bacteria. Its presence and characteristics are influenced by several variables, both in health as in illness. Nutrition is one of the important factors to consider and breastfeeding has a clear beneficial effect. Differences have been found in the characteristics of said flora between celiac and healthy individuals; there is as well a significant difference between untreated celiac patients and healthy adults, in celiac patients on GFD and in healthy adults, regarding acetic acid, propionic acid, butyric acid and all short-chained fatty acids.[96, 97] This raises an interesting and novel problem, since the use of probiotics can have a clearly beneficial effect in some of these patients, especially those with a partial response gluten-free diet or who have frequent relapses. Recent studies suggest that gut microbiota may play a role in some manifestations of celiac disease and these patients with gastrointestinal symptoms or anemia had lower microbial diversity than those with dermatitis herpetiformis.[98]

Chapter 25 describes the research design used in the preparation of a diary supplement with the addition of a probiotic (ES1) that has demonstrated to achieve a potent anti-inflammatory effect in in vitro studies and in experimental animals and being gluten-free, may be suitable for celiacs as nutritional support; it may also be used to improve and enhance the response to gluten-free diet, especially in patients with partial response or patients who have frequent relapses. There have been clinical trials in celiac and healthy controls, which have shown preliminary excellent results. This product is currently sold under the name of *Proceliac* by the *Central Lechera de Asturiana*.[99] Bakshi et al. discuss new treatments and include the use of probiotics with incorporated endopeptidases or transglutaminase inhibitors that could be used as GFD supplement and thus help patients to obtain a better quality of life.[100]

References

1. Dicke WK. *Treatment of celiac disease.* Ned Tijdschr Geneeskd. 1951; 95: 124-30.
2. De Re V, Caggiari L, Tabuso M, et al. *The versatile role of gliadin peptides in celiac disease*. Clin Biochem 2013; 46: 552-60. http://dx.doi.org/10.1016/j.clinbiochem.2012.10.038
3. Shiner M. *Jejunal-biopsy tube.* Lancet. 1956; 270: 85. http://dx.doi.org/10.1016/S0140-6736(56)92137-7
4. Shiner M. *Duodenal biopsy.* Lancet. 1956; 270: 17-9. http://dx.doi.org/10.1016/S0140-6736(56)91854-2
5. Kasarda DD, Okita TW, Bernardin JE et al. *Nucleic acid (cDNA) and amino acid sequences of alpha-type gliadins from wheat (Triticum aestivum).* Proc Natl Acad Sci USA. 1984; 81: 4712-6. http://dx.doi.org/10.1073/pnas.81.15.4712
6. Kristjansson G, Venge P, Hallgren R. *Mucosal reactivity to cow's milk protein in coeliac disease.* Clin Exp Immunol. 2007; 147: 449-55. http://dx.doi.org/10.1111/j.1365-2249.2007.03298.x
7. Di Sabatino A, Corazza GR. *Some clarification is necessary on the Oslo definitions for coceliac disease-related terms.* Gut 2013; 62: 182. http://dx.doi.org/10.1136/gutjnl-2012-302613
8. Di Sabatino A, Giuffrida P, Corazza GR. *Still Waiting for a Definition of Nonceliac Gluten Sensitivity.* J Clin Gastroenterol. 2013; febrero 18. http://dx.doi.org/10.1097/MCG.0b013e3182850dfe
9. Di Sabatino A, Corazza GR. *Nonceliac gluten sensitivity: sense or sensibility?* Ann Intern Med. 2012; 156: 309-11. http://dx.doi.org/10.7326/0003-4819-156-4-201202210-00010
10. Di Sabatino A, Vanoli A, Giufrrida P, et al. *The function of tissue transglutaminase in celiac disease*. Autoimmun Rev 2012; 11: 746:53.
11. Spence D. *Bad medicine: food intolerance.* BMJ. 2013; 346: f529. http://dx.doi.org/10.1136/bmj.f529
12. Ellis A, Linaker BD. *Non-coceliac gluten sensitivity?* Lancet 1978; 1: 1358-9. http://dx.doi.org/10.1016/S0140-6736(78)92427-3
13. Linaker BD, Calam J. *Is jejunal biopsy valuable in the elderly?* Age Ageing. 1978; 7: 244-5. http://dx.doi.org/10.1093/ageing/7.4.244
14. Hemmings WA. *Food allergy.* Lancet. 1978; 1: 608. http://dx.doi.org/10.1016/S0140-6736(78)91053-X
15. Jonas A. *Wheat-sensitive -but not coeliac.* Lancet. 1978; 2: 1047. http://dx.doi.org/10.1016/S0140-6736(78)92366-8
16. Dahl R. *Wheat sensitive - but not coeliac.* Lancet. 1979; 1: 43-4. http://dx.doi.org/10.1016/S0140-6736(79)90482-3
17. Cooper BT, Holmes GK, Ferguson R et al. *Gluten-sensitive diarrhea without evidence of celiac disease.* Gastroenterology. 1980; 79: 801-6.
18. Biesiekierski JR, Newnham ED, Irving PM et al. *Gluten causes gastrointestinal symptoms in subjects without celiac disease: a double-blind randomized placebo-controlled trial.* Am J Gastroenterol. 2011; 106: 508-14; quiz 515. http://dx.doi.org/10.1038/ajg.2010.487
19. Biesiekierski JRP, Peters SL, Newnham ED, Rosella O et al. *No Effects of Gluten in Patients with Self-Reported Non-Celiac Gluten Sensitivity Following Dietary Reduction of Low-Fermentable, Poorly-Absorbed, Short-Chain Carbohydrates.* Gastroenterology. 2013. http://dx.doi.org/10.1053/j.gastro.2013.04.051

20. Carroccio A, Brusca I, Mansueto P, It al. *A comparison between two different in vitro basophil activation tests for gluten- and cow's milk protein sensitivity in irritable bowel syndrome (IBS)-like patients.* Clin Chem Lab Med. 2012; 1-7.
21. Carroccio A, Mansueto P, Iacono G et al. *Non-celiac wheat sensitivity diagnosed by double-blind placebo-controlled challenge: exploring a new clinical entity.* Am J Gastroenterol. 2012; 107: 1898-906; quiz 1907. http://dx.doi.org/10.1038/ajg.2012.236
22. Sanders DS, Aziz I. *Non-celiac wheat sensitivity: separating the wheat from the chat!* Am J Gastroenterol. 2012;107:1908-12. http://dx.doi.org/10.1038/ajg.2012.344
23. Camilleri M, Kolar GJ, Vazquez-Roque MI, et al. *Cannabinoid receptor 1 gene and irritable bowel syndrome: phenotype and quantitative traits*. Am J Physiol Gastrointest Liver Physiol 2013; 304: G553-60. Camilleri M, Kolar GJ, Vazquez-Roque MI, et al. Cannabinoid receptor 1 gene and irritable bowel syndrome: phenotype and quantitative traits. Am J Physiol Gastrointest Liver Physiol 2013; 304: G553-60. http://dx.doi.org/10.1152/ajpgi.00376.2012
24. Vazquez-Roque MI, Bouras EP. *Linaclotide, novel therapy for the treatment of chronic idiopathic constipation and constipation-predominant irritable bowel syndrome*. Adv Ther. 2013; 30: 203-11. http://dx.doi.org/10.1007/s12325-013-0012-9
25. Vazquez-Roque MI, Camilleri M, Smyrk T et al. *A controlled trial of gluten-free diet in patients with irritable bowel syndrome-diarrhea: effects on bowel frequency and intestinal function.* Gastroenterology. 2013; 144: 903-11 e3. http://dx.doi.org/10.1053/j.gastro.2013.01.049
26. Sapone A, Bai JC, Ciacci C et al. *Spectrum of gluten-related disorders: consensus on new nomenclature and classification.* BMC Med. 2012; 10: 13. http://dx.doi.org/10.1186/1741-7015-10-13
27. Wahnschaffe U, Ignatius R, Loddenkemper C, et al. *Diagnostic value of endoscopy for the diagnosis of giardiasis and other intestinal diseases in patients with persistent diarrhea from tropical or subtropical areas*. Scand J Gastroenterol 2007; 42: 391-6. http://dx.doi.org/10.1080/00365520600881193
28. Wahnschaffe U, Schulzke JD, Zeitz M et al. *Predictors of clinical response to gluten-free diet in patients diagnosed with diarrhea-predominant irritable bowel syndrome.* Clin Gastroenterol Hepatol. 2007; 5: 844-50; quiz 769. http://dx.doi.org/10.1016/j.cgh.2007.03.021
29. Sapone A, Lammers KM, Mazzarella G et al. *Differential mucosal IL-17 expression in two gliadin-induced disorders: gluten sensitivity and the autoimmune enteropathy celiac disease.* Int Arch Allergy Immunol. 2010; 152: 75-80. http://dx.doi.org/10.1159/000260087
30. Sapone A, Lammers KM, Casolaro V et al. *Divergence of gut permeability and mucosal immune gene expression in two gluten-associated conditions: celiac disease and gluten sensitivity.* BMC Med. 2011; 9: 23. http://dx.doi.org/10.1186/1741-7015-9-23
31. Brottveit M, Beitnes AC, Tollefsen S et al. *Mucosal Cytokine Response After Short-Term Gluten Challenge in Celiac Disease and Non-Celiac Gluten Sensitivity.* Am J Gastroenterol. 2013; 108(5): 842-50. http://dx.doi.org/10.1038/ajg.2013.91
32. Akram S, Murray JA, Pardi DS et al. *Adult Autoimmune Enteropathy: Mayo Clinic Rochester Experience.* Clin Gastroenterol Hepatol. 2007; nov 5(11): 1282-90; quiz 1245. http://dx.doi.org/10.1016/j.cgh.2007.05.013
33. Bernardos E, Solis-Herruzo JA. *Autoimmune enteropathy.* Rev Esp Enferm Dig. 2003; 95: 494-6, 490-3.

34. Colletti RB, Guillot AP, Rosen S et al. *Autoimmune enteropathy and nephropathy with circulating anti-epithelial cell antibodies.* J Pediatr. 1991; 118: 858-64. http://dx.doi.org/10.1016/S0022-3476(05)82195-X
35. Murch SH, Fertleman CR, Rodrigues C et al. *Autoimmune enteropathy with distinct mucosal features in T-cell activation deficiency: the contribution of T cells to the mucosal lesion.* J Pediatr Gastroenterol Nutr. 1999; 28: 393-9. http://dx.doi.org/10.1097/00005176-199904000-00009
36. Lebwohl B, Granath F, Ekbom A, et al. *Mucosal healing and mortality in coeliac disease.* Aliment Pharmacol Ther. 2013; 37: 332-9.http://dx.doi.org/10.1111/apt.12164
37. Cerf-Bensussan N, Matysiak-Budnik T, Cellier C, et al. *Oral proteases: a new approach to managing coeliac disease*. Gut 2007; 56: 157-60. http://dx.doi.org/10.1136/gut.2005.090498
38. Marine M, Farre C, Alsina M et al. *The prevalence of coeliac disease is significantly higher in children compared with adults.* Aliment Pharmacol Ther. 2011; 33: 477-86. http://dx.doi.org/10.1111/j.1365-2036.2010.04543.x
39. Monzon H, Forne M, Gonzalez C, et al. *Mild enteropathy as a cause of iron-deficiency anaemia of previously unknown origin*. Dig Liver Dis. 2011; 43: 448-53. http://dx.doi.org/10.1016/j.dld.2010.12.003
40. Sollid LM, Qiao SW, Anderson RP et al. *Nomenclature and listing of celiac disease relevant gluten T-cell epitopes restricted by HLA-DQ molecules.* Immunogenetics. 2012; 64: 455-60. http://dx.doi.org/10.1007/s00251-012-0599-z
41. Junker Y, Zeissig S, Kim SJ et al. *Wheat amylase trypsin inhibitors drive intestinal inflammation via activation of toll-like receptor 4.* J Exp Med. 2012; 209: 2395-408. http://dx.doi.org/10.1084/jem.20102660
42. Di Sabatino A, Brunetti L, Carnevale Maffe G, et al. *Is it worth investigating splenic function in patients with celiac disease?* World J Gastroenterol 2013; 19: 2313-8. http://dx.doi.org/10.3748/wjg.v19.i15.2313
43. Di Sabatino A, Giuffrida P, Corazza GR. *From impending toxic megacolon to multiple organ failure in severe ulcerative colitis*. Intern Emerg Med. 2013; 8: 185-6. http://dx.doi.org/10.1007/s11739-012-0849-y
44. Di Sabatino A, Rovedatti L, Vidali F, et al. *Recent advances in understanding Crohn's disease*. Intern Emerg Med. 2013; 8: 101-13. http://dx.doi.org/10.1007/s11739-011-0599-2
45. Morita E, Chinuki Y, Takahashi H, et al. *Prevalence of wheat allergy in Japanese adults.* Allergol Int. 2012; 61: 101-5. http://dx.doi.org/10.2332/allergolint.11-OA-0345
46. Takahashi H, Matsuo H, Chinuki Y et al. *Recombinant high molecular weight-glutenin subunit-specific IgE detection is useful in identifying wheat-dependent exercise-induced anaphylaxis complementary to recombinant omega-5 gliadin-specific IgE test.* Clin Exp Allergy. 2012; 42: 1293-8. http://dx.doi.org/10.1111/j.1365-2222.2012.04039.x
47. Ebisawa M, Shibata R, Sato S et al. *Clinical utility of IgE antibodies to omega-5 gliadin in the diagnosis of wheat allergy: a pediatric multicenter challenge study.* Int Arch Allergy Immunol. 2012; 158: 71-6. http://dx.doi.org/10.1159/000330661
48. Kaptchuk TJ, Friedlander E, Kelley JM et al. *Placebos without deception: a randomized controlled trial in irritable bowel syndrome.* PLoS One. 2010; 5: e15591. http://dx.doi.org/10.1371/journal.pone.0015591
49. Raicek JE, Stone BH, Kaptchuk TJ. *Placebos in 19th century medicine: a quantitative analysis of the BMJ.* BMJ. 2012; 345: e8326. http://dx.doi.org/10.1136/bmj.e8326

50. Sanderson C, Hardy J, Spruyt O et al. *Placebo and Nocebo Effects in Randomized Controlled Trials: The Implications for Research and Practice.* J Pain Symptom Manage. 2013; in-press. http://dx.doi.org/10.1016/j.jpainsymman.2012.12.005
51. Benedetti F. *Placebo-induced improvements: how therapeutic rituals affect the patient's brain.* J Acupunct Meridian Stud. 2012; 5: 97-103. http://dx.doi.org/10.1016/j.jams.2012.03.001
52. Enck P, Benedetti F, Schedlowski M. *New insights into the placebo and nocebo responses.* Neuron. 2008; 59: 195-206. http://dx.doi.org/10.1016/j.neuron.2008.06.030
53. Benedetti F, Lanotte M, Lopiano L et al. *When words are painful: unraveling the mechanisms of the nocebo effect.* Neuroscience. 2007; 147: 260-71. http://dx.doi.org/10.1016/j.neuroscience.2007.02.020
54. Ludvigsson JF, Rubio-Tapia A, van Dyke CT et al. *Increasing Incidence of Celiac Disease in a North American Population.* Am J Gastroenterol. 2013; 108(5): 818-24. http://dx.doi.org/10.1038/ajg.2013.60
55. Ivarsson A, Myleus A, Norstrom F et al. *Prevalence of childhood celiac disease and changes in infant feeding.* Pediatrics. 2013; 131: e687-94. http://dx.doi.org/10.1542/peds.2012-1015
56. Lionetti E, Castellaneta S, Francavilla R, et al. *Introduction of gluten, HLA status, and the risk of celiac disease in children*. N Engl J Med. 2014; 371: 1295-303. http://dx.doi.org/10.1056/NEJMoa1400697
57. Vriezinga SL, Auricchio R, Bravi E, et al. *Randomized feeding intervention in infants at high risk for celiac disease*. N Engl J Med. 2014; 371: 1304-15. http://dx.doi.org/10.1056/NEJMoa1404172
58. Drago S, El Asmar R, Di Pierro M, et al. *Gliadin, zonulin and gut permeability: Effects on celiac and non-celiac intestinal mucosa and intestinal cell lines*. Scand J Gastroenterol 2006; 41: 408-19. http://dx.doi.org/10.1080/00365520500235334
59. El Asmar R, Panigrahi P, Bamford P, et al. *Host-dependent zonulin secretion causes the impairment of the small intestine barrier function after bacterial exposure*. Gastroenterology 2002; 123: 1607-15. http://dx.doi.org/10.1053/gast.2002.36578
60. Smecuol E, Sugai E, Niveloni S, et al. *Permeability, zonulin production, and enteropathy in dermatitis herpetiformis*. Clinical gastroenterology and hepatology: the official clinical practice journal of the American Gastroenterological Association 2005; 3: 335-41. http://dx.doi.org/10.1016/S1542-3565(04)00778-5
61. Klapp G, Masip E, Bolonio M, et al. *Celiac disease: the new proposed ESPGHAN diagnostic criteria do work well in a selected population*. J Pediatr Gastroenterol Nutr 2013; 56: 251-6. http://dx.doi.org/10.1097/MPG.0b013e318279887b
62. Kurppa K, Collin P, Viljamaa M et al. *Diagnosing mild enteropathy celiac disease: a randomized, controlled clinical study.* Gastroenterology. 2009; 136: 816-23. http://dx.doi.org/10.1053/j.gastro.2008.11.040
63. Esteve M, Rosinach M, Fernandez-Banares F et al. *Spectrum of gluten-sensitive enteropathy in first-degree relatives of patients with coeliac disease: clinical relevance of lymphocytic enteritis.* Gut. 2006; 55: 1739-45. http://dx.doi.org/10.1136/gut.2006.095299
64. Meresse B, Malamut G, Cerf-Bensussan N. *Celiac disease: an immunological jigsaw.* Immunity. 2012; 36: 907-19. http://dx.doi.org/10.1016/j.immuni.2012.06.006
65. Sollid LM, Jabri B. *Triggers and drivers of autoimmunity: lessons from coeliac disease.* Nat Rev Immunol. 2013; 13: 294-302. http://dx.doi.org/10.1038/nri3407

66. Cosnes J, Cellier C, Viola S et al. *Incidence of autoimmune diseases in celiac disease: protective effect of the gluten-free diet.* Clin Gastroenterol Hepatol. 2008; 6: 753-8. http://dx.doi.org/10.1016/j.cgh.2007.12.022
67. Zanini B, Caselani F, Magni A et al. *Celiac disease with mild enteropathy is not mild disease.* Clin Gastroenterol Hepatol. 2013; 11: 253-8. http://dx.doi.org/10.1016/j.cgh.2012.09.027
68. Korkut E, Bektas M, Oztas E et al. *The prevalence of celiac disease in patients fulfilling Rome III criteria for irritable bowel syndrome.* Eur J Intern Med. 2010; 21: 389-92. http://dx.doi.org/10.1016/j.ejim.2010.06.004
69. Giangreco E, D'Agate C, Barbera C et al. *Prevalence of celiac disease in adult patients with refractory functional dyspepsia: value of routine duodenal biopsy.* World J Gastroenterol. 2008; 14: 6948-53. http://dx.doi.org/10.3748/wjg.14.6948
70. Santolaria Piedrafita S, Fernandez Banares F. *Gluten-sensitive enteropathy and functional dyspepsia.* Gastroenterol Hepatol. 2012; 35: 78-88. http://dx.doi.org/10.1016/j.gastrohep.2011.10.006
71. Sainsbury A, Sanders DS, Ford AC. *Prevalence of Irritable Bowel Syndrome-type Symptoms in Patients With Celiac Disease: A Meta-analysis.* Clin Gastroenterol Hepatol. 2013; 11: 359-65 e1. http://dx.doi.org/10.1016/j.cgh.2012.11.033
72. Aziz I, Sanders DS. *The irritable bowel syndrome-celiac disease connection.* Gastrointest Endosc Clin N Am. 2012; 22: 623-37. http://dx.doi.org/10.1016/j.giec.2012.07.009
73. Malamut G, Meresse B, Cellier C, et al. *Refractory celiac disease: from bench to bedside.* Semin Immunopathol 2012; 34: 601-13. http://dx.doi.org/10.1007/s00281-012-0322-z
74. Tack GJ, van Wanrooij RL, Langerak AW et al. *Origin and immunophenotype of aberrant IEL in RCDII patients.* Mol Immunol. 2012; 50: 262-70. http://dx.doi.org/10.1016/j.molimm.2012.01.014
75. Rubio-Tapia A, Hill ID, Kelly CP et al. *ACG Clinical Guidelines: Diagnosis and Management of Celiac Disease.* Am J Gastroenterol. 2013; 108(5): 656-76. http://dx.doi.org/10.1038/ajg.2013.79
76. Lebwohl B, Granath F, Ekbom A, et al. *Mucosal healing and risk for lymphoproliferative malignancy in celiac disease: a population-based cohort study*. Ann Intern Med. 2013; 159: 169-75. http://dx.doi.org/10.7326/0003-4819-159-3-201308060-00006
77. Nachman F, del Campo MP, Gonzalez A et al. *Long-term deterioration of quality of life in adult patients with celiac disease is associated with treatment noncompliance.* Dig Liver Dis. 2010; 42: 685-91. http://dx.doi.org/10.1016/j.dld.2010.03.004
78. Casellas F, Rodrigo L, Vivancos JL et al. *Factors that impact health-related quality of life in adults with celiac disease: a multicenter study.* World J Gastroenterol. 2008; 14: 46-52. http://dx.doi.org/10.3748/wjg.14.46
79. Pico M, Spirito MF, Roizen M. *Quality of life in children and adolescents with celiac disease: Argentinian version of the specific questionnaire CDDUX.* Acta Gastroenterol Latinoam. 2012; 42: 12-9.
80. Paarlahti P, Kurppa K, Ukkola A et al. *Predictors of persistent symptoms and reduced quality of life in treated coeliac disease patients: a large cross-sectional study.* BMC Gastroenterol. 2013; 13: 75. http://dx.doi.org/10.1186/1471-230X-13-75
81. Dimitrova AK, Ungaro RC, Lebwohl B et al. *Prevalence of migraine in patients with celiac disease and inflammatory bowel disease.* Headache. 2013; 53: 344-55. http://dx.doi.org/10.1111/j.1526-4610.2012.02260.x
82. Ukkola A, Maki M, Kurppa K et al. *Diet improves perception of health and well-being in symptomatic, but not asymptomatic, patients with celiac disease.* Clin Gastroenterol Hepatol. 2011; 9: 118-23. http://dx.doi.org/10.1016/j.cgh.2010.10.011

83. Lee AR, Hong SW, Ju SJ. *Development of a scale to measure life transition process in parents of children with autism.* J Korean Acad Nurs. 2012; 42: 861-9. http://dx.doi.org/10.4040/jkan.2012.42.6.861
84. Lee AR, Ng DL, Diamond B et al. *Living with coeliac disease: survey results from the USA.* J Hum Nutr Diet. 2012; 25: 233-8. http://dx.doi.org/10.1111/j.1365-277X.2012.01236.x
85. Brottveit M, Vandvik PO, Wojniusz S et al. *Absence of somatization in non-coeliac gluten sensitivity.* Scand J Gastroenterol. 2012; 47: 770-7. http://dx.doi.org/10.3109/00365521.2012.679685
86. Richman E. *The safety of oats in the dietary treatment of coeliac disease.* Proc Nutr Soc. 2012; 71: 534-7. http://dx.doi.org/10.1017/S0029665112000791
87. Cooper SE, Kennedy NP, Mohamed BM et al. *Immunological indicators of coeliac disease activity are not altered by long-term oats challenge.* Clin Exp Immunol. 2013; 171: 313-8. http://dx.doi.org/10.1111/cei.12014
88. Comino I, Real A, Gil-Humanes J et al. *Significant differences in coeliac immunotoxicity of barley varieties.* Mol Nutr Food Res. 2012; 56: 1697-707. http://dx.doi.org/10.1002/mnfr.201200358
89. Real A, Comino I, de Lorenzo L et al. *Molecular and immunological characterization of gluten proteins isolated from oat cultivars that differ in toxicity for celiac disease.* PLoS One. 2012; 7: e48365. http://dx.doi.org/10.1371/journal.pone.0048365
90. Ronda F, Rivero P, Caballero PA et al. *High insoluble fibre content increases in vitro starch digestibility in partially baked breads.* Int J Food Sci Nutr. 2012; 63: 971-7. http://dx.doi.org/10.3109/09637486.2012.690025
91. Gibert A, Kruizinga AG, Neuhold S et al. *Might gluten traces in wheat substitutes pose a risk in patients with celiac disease? A population-based probabilistic approach to risk estimation.* Am J Clin Nutr. 2013; 97: 109-16. http://dx.doi.org/10.3945/ajcn.112.047985
92. Bosmans GM, Lagrain B, Ooms N et al. *Biopolymer interactions, water dynamics, and bread crumb firming*. J Agric Food Chem. 2013; 61: 4646-54. http://dx.doi.org/10.1021/jf4010466
93. Zarkadas M, Dubois S, MacIsaac K et al. *Living with coeliac disease and a gluten-free diet: a Canadian perspective.* J Hum Nutr Diet. 2013; 26: 10-23. http://dx.doi.org/10.1111/j.1365-277X.2012.01288.x
94. Gil-Humanes J, Piston F, Gimenez MJ et al. *The introgression of RNAi silencing of gamma-gliadins into commercial lines of bread wheat changes the mixing and technological properties of the dough.* PLoS One. 2012; 7: e45937. http://dx.doi.org/10.1371/journal.pone.0045937
95. Beckles DM, Tananuwong K, Shoemaker CF. *Starch characteristics of transgenic wheat (Triticum aestivum L.) overexpressing the Dx5 high molecular weight glutenin subunit are substantially equivalent to those in nonmodified wheat.* J Food Sci. 2012; 77: C437-42. http://dx.doi.org/10.1111/j.1750-3841.2012.02648.x
96. Caminero A, Nistal E, Arias L, et al. *A gluten metabolism study in healthy individuals shows the presence of faecal glutenasic activity.* Eur J Nutr. 2012; 51: 293-9. http://dx.doi.org/10.1007/s00394-011-0214-3
97. Nistal E, Caminero A, Vivas S et al. *Differences in faecal bacteria populations and faecal bacteria metabolism in healthy adults and celiac disease patients.* Biochimie. 2012; 94: 1724-9. http://dx.doi.org/10.1016/j.biochi.2012.03.025

98. Wacklin P, Kaukinen K, Tuovinen E et al. *The duodenal microbiota composition of adult celiac disease patients is associated with the clinical manifestation of the disease.* Inflamm Bowel Dis. 2013; 19: 934-41. http://dx.doi.org/10.1097/MIB.0b013e31828029a9
99. D'Arienzo R, Maurano F, Lavermicocca P et al. *Modulation of the immune response by probiotic strains in a mouse model of gluten sensitivity.* Cytokine. 2009; 48: 254-9. http://dx.doi.org/10.1016/j.cyto.2009.08.003
100. Bakshi A, Stephen S, Borum ML et al. *Emerging Therapeutic Options for Celiac Disease: Potential Alternatives to a Gluten-Free Diet.* Gastroenterol Hepatol (NY). 2012; 8: 582-588.