

CELIAC DISEASE IN CHILDREN AND ADULTS

FOR PHYSICIANS OF GENERAL MEDICINE AND PRIMARY CARE PAEDIATRICIANS

Quickly identify the symptoms of celiac disease.

Guide patients towards correct diagnosis.

Manage patients with the diagnosis



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INDEX

Preface: <i>G. Di Fabio, O. Lovello, M. Silano</i>	4
Epidemiology: <i>C. Catassi, E. Lionetti</i>	6
Pathogenic mechanisms: <i>A. Di Sabatino</i>	8
Clinical presentation in children: <i>R. Auricchio</i>	11
Clinical presentation in adults: <i>G.R. Corazza, F.Biagi</i>	14
Diagnosis: <i>M. Silano, U. Volta</i>	17
Complications: <i>F. Biagi</i>	22
Transition from child to adult: <i>T. Not</i>	24
Gluten-free diet and patient monitoring: <i>G. Guariso, A. Picarelli</i>	26
Autoimmunity and celiac disease: <i>R. Troncone</i>	28
Psychological aspects: <i>C. Ciacci, F.Zingone</i>	31
Regulatory aspects: <i>M. Silano</i>	34
Frontiers of research: <i>C. Gianfrani</i>	36

PREFACE

G. Di Fabio, AIC President; O. Lovello, FC President; M. Silano, Coordinator of the AIC-FC Scientific Committee

AIC Onlus (Italian celiac Association) is a non-profit patient association that has been committed **for over 35 years to positively changing the lives of people with celiac disease and their families**. It was founded in 1979 by a few parents of children with celiac disease at a time when little was known about it, and it was considered to be a disease linked to youth.

AIC is a federation composed of **20 associations** across all of the Italian regions, as well as in the autonomous provinces of Trento and Bolzano. **The Italian AIC network is one of its strengths.**

In addition to AIC, they are part of the AIC celiac Foundation, which provides grants for scientific research on the disease, and the social enterprise Spiga Barrata Service, which issues the trademark featuring the image of barred grain on the packaging of products suitable for those with celiac disease, and serves as the editor of publications that AIC creates for those with the disease and their families, such as Celiachia Notizie, Prontuario degli Alimenti, and Guida Alimentazione Fuori Casa.

AIC currently has more than 40,000 members and over 1,000 volunteers, who assist in pursuing AIC's mission on a daily basis.

The aim of the AIC is to allow celiacs or those with herpetiform dermatitis to live in a comfortably through the improvement of their lifestyle, supporting the acquisition of full awareness of their condition, and the widespread diffusion of proper knowledge as regards celiac disease and herpetiform dermatitis in society.

Why create a booklet on celiac disease and herpetiform dermatitis for physicians of general medicine and primary care paediatricians?

The booklet **"CELIAC DISEASE IN CHILDREN AND ADULTS"** is an informational and awareness initiative aimed at general practitioners and primary care paediatricians, who are generally the first line of identification for adults and children who have yet to receive the diagnosis of celiac disease. The main training and informational objectives of the booklet for physicians of general medicine and primary care paediatricians are to promptly identify the symptoms of celiac disease (often non-classic and extra-intestinal), guide patients towards correct diagnosis (often dealing with specialists), manage diagnosed patients by monitoring their treatment (gluten-free diet) and health status through specific examinations to be performed on a periodic basis.

In Italy, approximately 400,000 people are not aware that they have celiac disease. AIC is committed to assisting currently undiagnosed cases of the disease.

The celiac iceberg: It is estimated that there are 600,000 Italians with celiac disease, which is 1% of the population of Italy.

Undiagnosed celiac disease can lead to problems such as repeated spontaneous fractures in adults, repeated miscarriage, infertility, pregnancy disorders, iron deficiency or anaemia, in addition to more dramatic complications such as intestinal lymphoma.

On average, it takes six years from the onset of symptoms to arrive at a diagnosis.

AIC's commitment to diagnosis: Reducing the diagnosis time and the number of undiagnosed patients with celiac disease: patients and physicians play a fundamental role in recognising celiac disease in its various forms.

What AIC does, in practice:

1. creates awareness for physicians and informs patients with guidelines and informative material: Diagnosis protocol, Guide for Women & Celiac Disease, Celiac Disease Week
www.settimanadellaceliachia.it
2. spreads medical and scientific knowledge with the National AIC Congress, the biggest event on celiac disease in Italy for physicians and researchers, held every year in November
3. it supports the high-level scientific research on celiac disease in Italy: Over five years, the Celiac Foundation has financed 20 research projects for a total amount of 2,267,500 euros with annual research calls for tender.

DIAGNOSIS PROTOCOL AND FOLLOW-UP OF CELIAC DISEASE

An essential reference to the Booklet is the PROTOCOL FOR DIAGNOSIS AND THE FOLLOW-UP OF CELIAC DISEASE (published in Official Journal no. 191/2015), prepared by a panel of experts, which was requested by the Ministry of Health and directly involved several specialists of the AIC-FC Scientific Committee. The publication of the protocol in the Official Journal is an important step that was desired by the AIC in order to standardise the steps towards the diagnosis of celiac disease throughout Italy. The protocol defines celiac disease in its various currently known forms, and contains flow charts for the proper diagnosis and monitoring of patients with celiac disease. It is a useful and indispensable tool not only for specialists, but also for physicians of general medicine and primary care paediatricians who initially see patients with potential celiac disease and monitor their health status. The current position of the Ministry of Health on gluten sensitivity (recently also called sensitivity to wheat) is also provided, which is shared by the majority of those in the international scientific community.

It is possible to view and download diagnostic diagrams, one for the diagnosis of celiac disease in children and the other for adults, in addition to indications as to which examinations to perform during follow-up and at what time frames, at the following link: <http://www.settimanadellaceliachia.it/2016/diagnosi.html>

EPIDEMIOLOGY

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1 Is celiac disease rare?

Celiac disease is not rare: it is one of the most common non-curable human diseases. The high prevalence of celiac disease is primarily due to the ubiquitous spread of its primary causal factors: genetic predisposition (HLA-DQ2 and/or DQ8) and the consumption of gluten containing grains. In the past, celiac disease was considered a rare disorder and typical in children from Western countries. In the past, the diagnosis of celiac disease included only typical early-onset cases. Starting from the 1980s, the widespread availability of highly reliable serological tests has allowed the identifications of a much larger number of cases, which often feature atypical symptoms or none at all.

2 What is the frequency of celiac disease?

Current estimates of the prevalence of celiac disease in the general population based on highly reliable serological screening tests, such as the detection of anti-transglutaminase (tTG) IgA class antibodies, indicate an average frequency of 1%, with a variable range in the different populations from 0 to 6%. Data available from the literature seems to indicate a greater frequency of celiac disease in children as compared to adults, which can likely be correlated with the increase in the prevalence of the disease during recent decades (see answer to question no. 6).

3 Are there any differences as regards gender?

Similar to other autoimmune diseases, celiac disease is more frequent in women than men. The average ratio between women and men with celiac disease is 1.5-2:1. The reasons for this varying frequency with respect to gender remain unclear. This epidemiological data indicates the need for greater diagnostic attention in women, considering the potential effects of undiagnosed celiac disease on women's health (such as infertility, multiple miscarriages and osteoporosis).

4 Are there differences between different populations worldwide?

As previously mentioned, significant differences in the prevalence of celiac disease were found worldwide. The average frequency of celiac disease is 1% in Europe, but varies from 0.2% in Germany to over 2% in Scandinavia for reasons that are still not clear. Even wider variations have been observed on other continents, ranging from the absence of celiac disease in some East Asian populations such as those in Vietnam and Japan, to 5.6% in the Saharawi Arab population. In general, the frequency of celiac disease is directly proportional to the consumption of grain containing gluten in the general population and, to a lesser extent, to the frequency of genotypes that predispose to celiac disease.

5 What is the celiac iceberg?

The image of an iceberg is evoked when the extent of a phenomenon is much larger than that apparent. This concept can be well applied to celiac disease, since the real frequency of the disease is far superior to clinically “visible” cases, i.e. those diagnosed for the presence of well-defined clinical symptoms. Population screening surveys have shown that for every diagnosed case of celiac disease, there are at least 3-5 cases still undiagnosed, generally for the lack of clinical manifestations or for the presence of atypical symptoms. The increase in awareness of the clinical variability of celiac disease has led to an increase in the diagnosis of celiac disease, thus allowing the celiac iceberg more visible.

6 The incidence of celiac disease is on the raise?

Most recent epidemiological data show that the total frequency of celiac disease has increased in recent decades, especially in Western countries. In Italy, surveys carried out in the 1990s showed a prevalence of celiac disease in children of 0.7%, while current studies indicate that the incidence has nearly doubled in less than 30 years (currently, approximately 1.5%). The reasons for this worrying phenomenon are still unclear, but could be explained by several environmental changes, such as the variety of wheat used in food products, the quantity of gluten ingested, the method of leavening bread dough, changes in microbiota composition and other factors that remain unknown. In part, the increase observed depends on the improved performance of currently available diagnostic tests and widespread diagnostic attention to the disease.

7 What is the most appropriate strategy to identify persons affected by celiac disease?

According to experts, the most appropriate current diagnostic strategy is actively looking for celiac disease in all individuals who present risk factors. In detail, it is necessary to recommend looking for serological markers of celiac disease (anti-tTG antibodies) in all individuals with typical or atypical symptoms (see the chapter on symptoms) or in condition at high risk of disease, such as family history of celiac disease, autoimmune diseases and certain syndromes (such Down and Turner). This diagnostic strategy is technically defined as case-finding.

PATHOGENETIC MECHANISMS

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1 What is gluten, and why is it toxic for people with celiac disease?

Gluten is contained in grains widely used in food products, such as wheat, barley and rye. Gluten comprises a complex spectrum of proteins, mainly separated into two fractions: gliadins and glutenins. Some gluten epitopes are more immunogenic than others. In particular, the most immunogenic fragment is the 33-mer immunodominant peptide, which consists of 33 amino acids of the α -gliadin fraction and has six partially overlapping DQ2-restricted epitopes, since it contains a large number of residual proline and glutamine. Proline offers both proteolysis resistance as well as a helix shape, which is able to strengthen the bond with HLA-DQ2 and HLA-DQ8 molecules expressed by the antigen-presenting cells. Glutamine is a preferred substrate for deamidation supported by tissue transglutaminase, thus increasing the immunogenicity of gluten itself. In this way, the immune activation of T lymphocytes is supported, which leads to the development of histological lesions that are typically seen in celiac disease: atrophy of the villi, crypt hyperplasia and intraepithelial lymphocytosis.

2 What factors other than gluten can play a role in promoting the development of celiac disease?

Several factors other than gluten have been implicated in the development of celiac disease. First, the disease is HLA-restricted, meaning that only HLA-DQ2 and DQ8-positive individuals can develop it. At least 41 gene variants (risk loci) other than HLA genes - and often with regulatory immune functions - may increase the risk of developing the disease. In particular, regulating genes of T-lymphocyte maturation and cytokine-encoding genes (IL-2 and IL-21) are involved. However, at present there is not enough evidence to support systematic genetic screening. Finally, the role of viral infections (rotavirus, adenovirus), the use of antibiotics, and type of delivery (natural vs caesarean) is not yet fully defined.

3 What mechanisms are activated in the intestinal mucosa of patients with celiac disease that lead to atrophy of the villi following the ingestion of gluten?

Gluten peptides pass through the intestinal epithelium at a paracellular level or through retro-transcytosis. Once in the lamina propria, they are deamidated by tissue transglutaminase, which results in greater immunogenicity that enhances the presentation of dendritic cells to T-lymphocyte cells. Following their activation, the latter produce abundant amounts of pro-inflammatory cytokines, such as interferon (IFN)- γ and IL-17A. IFN- γ supports the secretion of matrix metalloproteases, enzymes that degrade the extracellular matrix and basal membrane by the myofibroblasts and mononuclear cells of the lamina propria, and increases the cytotoxicity of intraepithelial lymphocytes. In turn, the latter support the apoptosis of enterocytes, which is supported by the Fas/Fas ligand system, with perforin-granzyme and the interaction between the NKG2D receptor and class HLA I ligand. Enterocytic apoptosis causes the atrophy of villi in the intestinal mucosa of patients with celiac disease.

4 As they are commonly used in the diagnosis of this condition, do antibodies specific to celiac disease have a pathogenetic significance?

Antibodies used to diagnose celiac disease (anti-tTG/anti-endomysium, EMA) do not have a direct or predominant pathogenetic role. Rather, tTG plays an important role in gluten deamidation, rendering it more accessible to antigen-presenting cells. Once gluten reaches the lamina propria, it is deamidated by this enzyme, becoming rich in glutamate residues (which have a negative charge), thus increasing its attraction to HLA-DQ2 and DQ8. There is little evidence that shows that anti-tTG antibodies can activate: a) mesenchymal cells of the intestinal mucosa (increasing the degradation of the extra-cellular matrix), b) monocytes (inducing the production of cytokines) and c) angiogenesis at the level of the small intestine (leading to disorganised vascular growth). However, the meaning of all of these alterations has not yet been clearly defined.

5 Is it possible to re-induce gluten tolerance in patients with celiac disease by means of modulation of the immunological mechanisms that trigger intestinal damage?

The use of a desensitising vaccine (such as those used for allergic diseases) is currently being studied, with the aim of reprogramming the physiological tolerance of T cells, so as to render them innocuous even if the patient ingests gluten. This vaccine contains the three most immunogenic fragments of gluten. Its long-term efficacy on humans has yet to be tested, and it is not currently available. If studies confirm the efficacy and safety of this vaccine, it would be the first medical treatment for celiac disease.

6 What are the mechanisms involved in the evolution of uncomplicated celiac disease to the refractory form or intestinal lymphoma?

The interaction between CD40 and CD40 ligand (CD40L), expressed by dendritic cells and T lymphocytes, seems to play a key role in both uncomplicated celiac disease and its refractory form. In patients with refractory celiac disease, there is a marked increase of IL-6 and TNF- α , unlike uncomplicated celiac disease. The pro-inflammatory cytokine IL-15 produced by epithelial cells and dendritic cells plays a pro-lymphomagenic role in celiac disease, although the mucosal levels of IL-15 do not vary between uncomplicated celiac disease and its refractory form. IL-15 supports the cytotoxicity of intraepithelial lymphocytes against epithelial cells, inducing apoptosis mediated by the perforin-granzyme system and the interaction between the NKG2D receptor and class HLA I ligand. Moreover, IL-15 inhibits the apoptosis of intraepithelial lymphocytes and promotes the emergence of proliferating clones, which promote the onset of intestinal lymphoma. It has been suggested that a duodenal infection of Epstein-Barr Virus contributes to lymphomagenesis.

7 Are non-invasive molecular biomarkers able to identify the slatentisation of mucosal lesions in potential form or predict development towards intestinal lymphoma in the refractory form?

Currently, there are no non-invasive molecular biomarkers able to identify the development of mucosal lesions in potential form or predict evolution towards intestinal lymphoma in the refractory form. Therefore, patients with potential celiac disease who are on a free diet must undergo annual endoscopic follow-up with well-oriented duodenal biopsies. Similarly, patients with refractory celiac disease must undergo an annual esophagogastroduodenoscopy with well-oriented duodenal biopsies, phenotypic characterisation of intraepithelial lymphocytes, and clonality study of the T cell- γ receptor.

8 Are there any molecular targets whose therapeutic neutralisation is able to stop the progression of complicated celiac disease?

Type 1 refractory celiac disease can benefit from steroids such as prednisone or budesonide, potentially in combination with immunomodulators such as azathioprine, 6-mercaptopurine or tacrolimus. On the other hand, type 2 refractory celiac disease is much less responsive to steroids and immunomodulators. Therefore, the main therapeutic options in type 2 refractory celiac disease include cladribine, anti-CD52 alemtuzumab antibody, or high-dose chemotherapy followed by autologous stem cell transplantation. Additional molecular targets could be TNF- α and IL-15, where both the anti-TNF- α infliximab and anti-IL-15 were theorised as potential new therapeutic options.

9 What are the pathophysiological mechanisms involved in the pathogenesis of the main extra-intestinal manifestations of celiac disease?

Dermatitis herpetiformis (DH) is the most known extra-intestinal manifestation of celiac disease. It is caused by the depositing of type A immunoglobulins at a cutaneous level (at the apex of the dermal papillae), induced by the ingestion of gluten. These patients have the same characteristics found in celiacs, namely the HLA-DQ2 and DQ8 restriction and response to a gluten-free diet. Significant neutrophilic infiltrate is present at the cutaneous level, induced by the increase in IL-8. Specific antibodies to the level of the dermis are also present: anti-tTG 3 antibodies. Other extra-intestinal manifestations may be related to substance malabsorption, such as iron deficient anaemia (iron deficiency) and osteoporosis (calcium deficiency).

10 Is intestinal microbiota altered in the presence of celiac disease?

Only a few high-quality studies have been performed on intestinal microbiota and celiac disease. From preliminary data, it appears that the microbiota varies both in treated and untreated celiac disease, compared to healthy controls. In particular, Firmicutes and Bifidobacteria decrease, while Proteobacteria, Bacteroides, and *E. coli* increase. However, it is not known whether these changes are a cause or consequence of celiac disease. The gluten-free diet is often also low in fibre, and could therefore influence the composition of the microbiota.

11 What are the pathogenic differences between celiac disease and non-celiac gluten sensitivity?

Celiac disease is supported by the adaptive and innate immunity triggered by gluten in genetically susceptible individuals. Non-celiac gluten sensitivity (NCGS) was initially thought to be a condition of innate immunity, although mucosal increases in the main cytokines of innate immunity have not been recently proven. The main limitation of the studies lies in the fact that the results were found in patients not subjected to a double-blind gluten-controlled oral challenge test versus placebo, or in patients without symptoms in keeping with true non-celiac gluten hypersensitivity. However, the pathogenesis of NCGS seems to be much more heterogeneous, as gluten increases intestinal fermentation, alters intestinal peristalsis on the basis of its simi-opioid characteristics, and may offer a placebo effect. In addition to gluten, wheat contains two other elements that could trigger symptoms: carbohydrates, such as oligosaccharides, disaccharides, monosaccharides and fermentable polyols, and other proteins, such as amylase/trypsin inhibitors.

CLINICAL PRESENTATION IN CHILDREN

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1 How has the clinical framework changed in the last 10 years as regards diagnosis? Has the age of onset changed?

Celiac disease can also show a broad spectrum of clinical manifestations in children. The so-called classical form usually occurs between 6 months and 2 years of life, shortly after weaning, with the failure to thrive, chronic diarrhoea, abdominal distension, asthenia, muscular hypotonia, lack of appetite and irritability. Rarely is a "celiac crisis" seen nowadays, characterised by explosive watery diarrhoea, marked abdominal distension, dehydration, de-electrolysis, hypotension and lethargy. In recent years, there has been a gradual delay in the onset of clinical manifestations of celiac disease in adolescents. These children have usually intestinal symptoms, such as recurrent abdominal pain, constipation or extra-intestinal symptoms such as short stature, delay of puberty, iron-deficiency anaemia, alopecia, aphthous stomatitis, dental enamel defects, and increased transaminases. A wide range of neurological and psychiatric disorders, such as epilepsy with occipital calcifications, ataxia, hypotonia, mental retardation, learning disabilities, attention deficit, and migraines has been described in association with celiac disease in children. An increasing number of studies have shown that many conditions associated with celiac disease (which were originally described in adults) can also be observed in children and adolescents, such as reduction of bone mass (osteoporosis); this usually easily regresses with a gluten-free diet.

2 Is there a correlation between clinical framework and intestinal damage?

The damage generated at an intestinal level for children with celiac disease is a slow and gradual process; the mechanism that causes the severity of the clinical manifestations of the disease is still unknown. Various studies have shown that neither the degree of villous atrophy nor the extent of enteropathy assessed by videocapsulation correlates with clinical symptomatology. These data must be supported by more accurate histological analyses, such as morphometry, to quantify mucosal damage, CD3 + intraepithelial lymphocyte counts and the collection and analysis of multiple biopsies in order to establish the presence of zonal differences in the severity of intestinal damage. A recent Finnish study has shown that the ratio of villous height/crypt depth, rather than the number of CD3+ lymphocytes infiltrating the intestinal epithelium, correlates well with gastrointestinal symptoms and laboratory tests (anti-transglutaminase antibodies) in the diagnosis of the disease.

While on the other hand there is no agreement on the relationship between HLA and clinical manifestations, otherwise there is no doubt that the dose of HLA affects the risk of developing the disease, and is linked to a greater reactivity of T lymphocytes.

3 Is the clinics different between screened patients and those identified with case-finding?

Celiac disease has become one of the main public health issues worldwide, as its prevalence has increased in almost every country over the last 20 years. Because clinical manifestations vary widely, there are a considerable number of undiagnosed patients. In addition, the availability of practical and reliable serological tests has repeatedly challenged the usefulness of mass screening activities. The benefits of such a strategy remain controversial, especially because one wonders what degree of adherence to the gluten-free diet would be in persons for which the diagnosis is made during screening and without obvious symptoms. To try to answer these questions, a study was conducted that compared symptoms, serology and histology upon diagnosis and after 3, 6, 12 and 48 months of a gluten-free diet in celiac children (the two groups did not differ by gender and age). The authors showed that even patients diagnosed via mass screening activities complained of symptoms (51.8%), although not always clear, while anaemia and growth retardation were more frequent in this group. No difference was then detected regarding serology and histology at the time of diagnosis.

4 Potential celiac disease: different clinical framework? How are they treated? What are the atrophy risk factors?

Potential celiac disease represents around 10% of the diagnoses given in this area. In most cases, they are asymptomatic children belonging to risk categories. Even today, there is no unanimous agreement on the dieto-therapeutic management of these patients, if they should be put on a gluten-free diet (10) or only those that are symptomatic. Prospective cohorts have shown that a percentage of these patients are left without a specific diet, because they are asymptomatic and became seronegative, while another group,

which varies in percentage for children and adults, develops a atrophy over the years.

In seeking to identify risk factors already evident at the time of diagnosis associated with the development of intestinal damage, it was shown that the genetic risk class (in particular, homozygosity for DQ2) and the degree of inflammation of the duodenal mucosa (Marsh grade 1) seem to more often correlate with intestinal atrophy.

5 Is it possible to theorise preventive strategies for children at risk?

The primary prevention of celiac disease, which completely avoids the appearance of the disease, is not yet possible. What we can do today is identify the categories of subjects at risk of having celiac disease through the careful analysis of data supplied to us by literature, and make sure to diagnose these subjects in advance before the disease clinically manifests.

Recent studies on risk cohorts (newborns with a first-degree relative with celiac disease) followed prospectively from birth have clarified that both breastfeeding and the time of introduction of gluten (both early at 5-6 months, as well as late, after one year of life) have no effect on the development of the disease. It has also been confirmed that homozygosity for DQ2 and the female gender are two factors that significantly increase the risk of having celiac disease.

Among the other risk factors involved, infections that are contracted in the early years of life seem to play a role of increasing importance, and not only those that are strictly gastrointestinal. A recent Italian study has shown that respiratory infections in the first two years of life, and having a father with celiac disease considerably increases the risk of developing it early on in life.

CLINICAL PRESENTATION IN ADULTS

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1 How does celiac disease usually present?

Celiac disease, which until the mid-1980s was only taken into consideration in the presence of symptoms of malabsorption such as diarrhoea, steatorrhea, weight loss and nutritional deficiency, currently has a much more nuanced presentation, presenting milder gastrointestinal symptoms that are very often extraintestinal. Gastrointestinal symptoms have characteristics of duration and intensity that so closely resemble those of the irritable bowel syndrome that a previous diagnosis of the latter condition is a significant cause of diagnostic delay. Patients can also be diagnosed for the detection of iron deficiency anaemia, osteoporosis and other conditions and symptoms due to the malabsorption of individual nutrients. It is also very important that the diagnosis can also be suggested by one of the many autoimmune (and non-autoimmune) diseases that are currently known to be associated with celiac disease (see FAQ No. 5). Some patients are diagnosed without having any symptoms. This is the case of subjects diagnosed due to a screening of first-degree family members or in the general population.

2 When does the onset of celiac disease occur?

As demonstrated by studies performed several years ago, the age of onset of celiac disease in adults has a dual presentation. The age at diagnosis of women is usually between the third and fourth decade of life, while for men it is between the fourth and fifth decade. Having said this, it must however be immediately stated that more advanced age is absolutely not a criterion for excluding the diagnosis of celiac disease that, in the presence of a suggestive clinical framework, will instead always be carefully examined. It is precisely in patients diagnosed at an advanced age that the complications of celiac disease have the highest incidence, whose onset drastically worsens the prognosis of these patients.

3 What do the terms classical/major, non-classical/minor, and silent/asymptomatic celiac disease mean?

We refer to classical/major celiac disease when the patient is diagnosed due to the presence of clinical framework characterised by diarrhoea, steatorrhea and weight loss, and symptoms of overall malabsorption syndrome due to the inability of the small intestine to absorb a large part of nutrients. Obviously, these patients can also present nutritive deficits due to the selective malabsorption of one or more micronutrients.

For non-classical/minor celiac disease, we mean the form of celiac disease that is diagnosed in the presence of minor, transient and extraintestinal gastrointestinal symptoms. This is the case of patients who are diagnosed, for example, with iron deficiency anaemia due to iron malabsorption or osteoporosis due to calcium malabsorption. All patients with celiac disease who have been diagnosed as suffering from

autoimmune diseases known to be associated with celiac disease are also considered affected by this form of celiac disease (see point 5).

Lastly, silent/asymptomatic celiac disease is when the patient is diagnosed in the absence of symptoms. In most cases, this occurs in patients diagnosed due to screening of first-degree family members or general population screening activities.

4 What do potential celiac disease and latent celiac disease mean?

By potential celiac disease, we mean a form characterised by a pathological framework with duodenal mucosa that is not yet atrophic (but with an increase in intraepithelial lymphocytes) and endomysial-positive antibodies. The clinical framework is variable, as since it can be included among the major, minor or silent forms of celiac disease (point 3). The writer retains that the presence of endomysial antibodies is a "conditio sine qua non" to be able to make such a diagnosis. The finding of negative endomysial but positive transglutaminase antibodies is not sufficient, and should be considered a false positive in the presence of a non-atrophic duodenal mucosa.

Potential celiac disease is an uncommon condition (10-15% of all patients with celiac disease) and poses significant patient management problems. It is not yet clear whether it is preferable to immediately start a gluten-free diet or to start a follow-up. The authors believe that it is difficult to give valid guidelines for patients as a whole, but that the decision should be made on a case-by-case basis. For this reason, these patients should be sent to tertiary referral centres for celiac disease.

The term latent celiac disease has instead been used with different meanings. According to some authors, it is used to convey a condition characterised by the finding of normal duodenal mucosa in a patient on a diet containing gluten in which the atrophy of villi has been previously demonstrated. Others have instead used this term to retrospectively define a normal duodenal biopsy in a patient who had or will then develop atrophy of the villi. In other cases it has been used as a synonym of potential celiac disease, silent celiac disease, celiac disease preceded by autoimmune diseases or even undiagnosed celiac disease. The reader hence understands that this is a very confusing term, of which it is not easy to understand the meaning attributed to it by the person who wrote it, and which would therefore be better if avoided altogether.

5 What are the pathological conditions in which concomitant celiac disease should be excluded?

The pathological conditions in which concomitant celiac disease must be excluded are represented by a series of autoimmune and non-autoimmune conditions. This is the case of DH, primary biliary cholangitis, alopecia areata, autoimmune thyopathy, autoimmune neuropathy, Addison's disease, atopy, IgA nephropathy, ulcerative colitis, idiopathic dilatative cardiomyopathy, IgA selective deficiency, Sjögren syndrome, juvenile idiopathic arthritis, type I diabetes mellitus, polymyositis, autoimmune hepatitis, cutaneous and systemic vasculitides, sclerosing cholangitis, and Down syndrome. It is important to remember that celiac disease should always be excluded in all these conditions, regardless of the

presence or absence of gastrointestinal symptoms. The start of a rigorous gluten-free diet in these patients is important not only for the unrecognised celiac disease, but also for the associated disease that led to the diagnosis of celiac disease, even if only for the improvement of intestinal absorption of p.o. drugs.

6 Can I suspect celiac disease in a subject without gastrointestinal symptoms?

Celiac disease can never be excluded on the basis of clinical criteria only. The presence of one of the diseases listed in FAQ no. 5 or other conditions that form the framework of minor or silent celiac disease (FAQ no. 3) are more than enough to suspect celiac disease and start a proper diagnostic process.

7 Is there any group of patients in whom celiac disease can be excluded on the basis of clinical symptoms only? Obese patients? Patients with constipation? Elderly patients?

Celiac disease can never be excluded at a clinical level. Although conditions such as obesity, constipation and advanced age make a diagnosis of celiac disease more unlikely, it cannot be excluded in the presence of other symptoms that suggest celiac disease. Although celiac disease is certainly not the first pathological condition that a physician must consider in a patient who develops constipation, weight loss and anaemia, it should also be considered and excluded after that intra-abdominal neoplastic pathologies have been excluded.

8 What about relatives of patients with celiac disease?

First-degree relatives of patients with celiac disease have a 15-20% risk of being affected by celiac disease themselves. Therefore, every time a new diagnosis of celiac disease is made, the guidelines of the Ministry of Health indicate to inform the patient of this risk, and to recommend to screen all first-degree family members with tTG antibodies. The HLA typing of first-degree relatives has also been suggested. This is to select HLA-compatible patients with celiac disease (DQ2 or DQ8-positive) from non-HLA compatible patients. This with the aim of monitoring only at risk of developing celiac disease. Considering that the number of negative DQ2 and DQ8 family members is reduced (20-30%), that even the HLA test may provide false negatives, that the incidence of celiac disease in first-degree family members who are already negative for anti-transglutaminase is very low, the writer is not sure that this expensive strategy is preferable to a simple antibody assay to be carried out every two years in the absence of symptoms.

DIAGNOSIS

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1 What is the correct use and how should antibody tests be interpreted in the various clinical situations (general population, groups at risk and malabsorption)?

Markers for the diagnosis of celiac disease are IgA anti-tTG antibodies (sensitivity 98%, specificity 90%) and IgA class EMA (sensitivity 95%, specificity approximately 100%). Because of their absolute specificity, EMAs are used as tests to confirm that the positivity for anti-tTG antibodies, as they are an effective marker for celiac disease. The third serological marker is the antibody to the deamidated peptides of gliadin (DGP), which has a lower sensitivity and specificity than the anti-tTG and EMA. In mass screening, anti-tTG antibodies should be performed, followed by EMA in anti-tTG positive cases, with duodenal biopsy in cases with dual antibody positivity. Patients in risk groups should be tested for anti-tTG or EMA antibodies; if they are positive, they should undergo a duodenal biopsy. In patients with severe malabsorption, a duodenal biopsy should be performed independently of the outcome of the antibodies. In all subjects studied for celiac disease, selective IgA deficiency should be excluded by seeking the total serum IgA; it is a condition associated with celiac disease that provides a different serological approach.

2 What tests should be used for celiac disease screening in early childhood and in patients with selective immunoglobulin A deficiency?

Selective IgA deficiency is a condition associated with celiac disease. The diagnostic procedure to identify celiac disease in patients with IgA deficiency involves the detection of class IgG antibodies. Both anti-tTG IgG and anti-DGP IgG antibodies have high sensitivity ($\geq 90\%$). If one of the above tests is positive, the diagnosis of celiac disease will be confirmed with a duodenal biopsy. It should be noted that, in patients with IgA deficiency and clinical signs of malabsorption, a duodenal biopsy should be performed even if the anti-tTG IgG and anti-DGP IgG antibodies are negative, since neither test is capable of identifying 100% of cases of celiac disease in the presence of low or absent serum IgA.

The most valid test for the diagnosis of celiac disease in children <2 years old is that of IgG anti-DGP antibodies. These are the first antibodies that are positivised when celiac disease develops, preceding the appearance of anti-tTG. Therefore, in children under the age of 2 years with suspected celiac disease, it is advisable to carry out anti-DGP IgG antibody screening first, or perform the screening even if the anti-tTG IgA is negative.

3 What serological tests should be used in monitoring patients with celiac disease?

Serological tests are extremely useful in the diagnostic route of celiac disease, but are of limited importance in follow-ups. The two tests that are used to monitor adherence to a gluten-free diet are the anti-tTG IgA and anti-DGP IgG antibodies. Anti-tTG IgG or DGP IgG can be used indifferently in patients with IgA deficiency. The negativisation of these markers during a gluten-free diet does not guarantee that the intestinal mucosa has normalised, while the persistence of antibody positivity with high titres is almost certainly an absolute expression of non-adherence to the diet and persistence of severe lesions of the intestinal wall.

4 Duodenal biopsy: which patients should undergo this test, at which locations should biopsies be performed, how many biopsies should be performed, and what are the criteria to be respected for the proper preparation and interpretation of the histological preparation?

The biopsy is the diagnostic gold standard. According to the ESPGHAN guidelines, the diagnosis can be made without a biopsy in symptomatic children/adolescents with high antibody titres and positive genetics. The biopsy is performed in the presence of serological markers and in all cases with malabsorption, regardless of blood results. The number of biopsies must be of a number not less than 4 (2 in the bulb, 2 in the distal duodenum). The orientation of the biopsy is fundamental for proper evaluation. The classification of Marsh-Oberhuber identifies: non-atrophic lesions (grade 1 and 2) with increased intraepithelial lymphocytes, with or without hyperplasia of the crypts (compatible with potential celiac disease in the presence of positive serology and genetics), and the atrophy of villi (grade 3) (with a villi/crypt ratio up to 1:1), which is subdivided into light (3a), partial (3b) and subtotal (3c) according to severity. Corazza and Villanacci proposed to divide the lesions into non-atrophic (grade A) and atrophic (grade B); grade B was then subdivided into B1, in which the villi are still identifiable, and B2, in which the villi are completely atrophic.

5 Which genetic test should be performed and when? Indications and interpretation of results.

The genetic test for celiac disease consists of the determination of the presence of alleles of the major histocompatibility system of class II (or HLA) DQ2 and DQ8. These alleles are the main and mandatory determinants of a genetic predisposition to celiac disease. Positivity to DQ2 or DQ8 alone is not sufficient to diagnose celiac disease. These alleles are present in 30-40% of the general population, while the development of celiac disease is only seen in 1% of cases. The genetic test for celiac disease has a highly negative predictive value. In the event of negativity to both haplotypes, the risk of developing celiac disease is practically nil, whereas if positive, the diagnosis must be ascertained with serology and potentially with a duodenal biopsy. In clinical practice, the performance of this test should be reserved for at-risk populations, such as first-degree relatives of celiacs, people with autoimmune diseases related to celiac disease, patients with chromosomal abnormalities (Down syndrome, Turner syndrome, Williams syndrome), those with an uncertain diagnosis or with a previous diagnosis to be confirmed, and children who fall into the selected population who can avoid duodenal biopsy for diagnosis pursuant to the ESPGHAN recommendations.

6 Flat mucosa with negative serology: how to establish the differential diagnosis between seronegative celiac disease and other causes of non-gluten-related atrophy of villi

Intestinal villi atrophy with anti-tTG and EMA positive antibodies confirms the diagnosis of celiac disease. However, it can occur in patients who have atrophy of the villi with negative serology. Many of these patients have seronegative celiac disease, but a differential diagnosis should be considered with other conditions that cause atrophy of the villi, such as infectious diseases, autoimmune enteropathy, variable common immunodeficiency, pharmaceutical enteropathy, bacterial contamination syndrome of the small intestine, Whipple disease, Crohn's disease, eosinophilic gastroenteritis and intestinal lymphoma. In this perspective, the first test to be performed is a screening for HLA-DQ2 and -DQ8. If this test is negative, the diagnosis of celiac disease can be ruled out. If the genetics are positive, before starting the gluten-free diet it is necessary to exclude all of the other diseases listed above by means of appropriate screenings. Once these are excluded, the patient will start a trial gluten-free diet that will confirm the diagnosis of celiac disease if a good clinical response is obtained, and regrowth of villi in the biopsy performed after at least 12 months of a gluten-free diet.

7 Which diagnostic protocol is to be used for patients with severe malabsorption?

Severe malabsorption is characterised by marked weight loss with repeated diarrhoea. The patient presenting this clinical framework complains of marked asthenia and an absorption deficit affecting both the mucosal structure and absorption of folic acid and vitamin D, which are all substances that are absorbed in the small intestine. The diagnostic procedure in a patient with these characteristics is to immediately proceed with the execution of esophagogastroduodenoscopy with multiple duodenal biopsies regardless of the outcome of the serological tests, not only to verify the presence of celiac disease, but also to shed light on other potential diseases that cause malabsorption and health impairment in general.

8 Which diagnostic protocol should be used in a patient that is already on a gluten-free diet without having previously excluded the diagnosis of celiac disease?

In the event that it is necessary to confirm the diagnosis of celiac disease when a gluten-free diet has already been started, follow the protocol below:

PHASE	ADULT	PEDIATRIC (up to 16 years of age) <i>avoid the reintroduction of gluten in the period immediately prior to puberty</i>
1	Evaluate genetics. If the subject is DQ2/8 positive, proceed with the following steps	Evaluate genetics. If the subject is DQ2/8 positive, proceed with the following steps
2	3 months of no specific diet (at least 1 portion of food containing gluten - bread, pasta, pizza, biscuits, sandwiches - during the 3 main meals) unless the appearance of major symptoms occurs	6 weeks of no specific diet (at least 1 portion of food containing gluten - bread, pasta, pizza, biscuits, sandwiches - during the 3 main meals) unless the appearance of major symptoms occurs
3	Serology (anti-tTG ab)	Serology (anti-tTG ab)
4	<p>A. If symptoms and/or serology are positive, perform an intestinal biopsy.</p> <p>B. If serology is negative, continue the patient's serological and clinical monitoring (every 2 months during the first year, then every 6 months) for a period of time at the discretion of the clinician, continuing with a non-specific diet.</p>	<p>A. If symptoms and/or serology are positive, perform an intestinal biopsy.</p> <p>B. If serology is negative, continue serological and clinical monitoring of the patient (every 2 months during the first year, then every 6 months) for a period of time at the discretion of the clinician, continuing with a non-specific diet. The diagnosis of celiac disease is made if the child has two of the following: suggestive symptoms, positive serology, villous atrophy.</p>

9 What are the diagnostic criteria to be used for the correct diagnosis of potential celiac disease, and what is the suggested therapeutic approach?

The criteria to be met for the correct diagnosis of potential celiac disease are: 1) positive serological markers of celiac disease (anti-tTG and EMA antibodies); 2) positive genetic test: HLA-DQ2 and/or -DQ8; 3) normal intestinal mucosa or with increased intraepithelial lymphocytes (> 25/100) (Marsh 0-1). Clinical celiac disease can be symptomatic or asymptomatic. Following the performance of serological screening for celiac disease in recent years, there has been a significant increase in diagnoses of celiac disease, which currently account for approximately 15% of total diagnoses. Which therapeutic approach should be used in cases of potential celiac disease? Since there are no well-defined guidelines, treatment must be decided on a case-by-case basis.

10 How are the ESPGHAN criteria applied for diagnosing children in order to avoid critical issues and diagnostic errors?

The ESPGHAN criteria establish that in a selected paediatric population with anti-tTG antibody levels higher than 10 times the cut-off, duodenal biopsy can be avoided for the diagnosis of celiac disease as long as all of the following are present, in addition to the aforementioned antibody levels: positivity of the EMA, positivity of genetic testing, and the presence of symptoms that suggest celiac disease. The ESPGHAN criteria are specific for children, and should not be applied to the diagnosis in adults, for which it is still mandatory to perform a duodenal biopsy for issues related to differential diagnosis and to exclude complications of celiac disease. If the four criteria are not met, or if the attending physician deems it appropriate based on evaluation, the diagnosis can be confirmed with a duodenal biopsy for children when the ESPGHAN criteria are met. The persistence of symptoms and/or antibody positivity after the diagnosis and the consequent beginning of the gluten-free diet is an indication to perform a duodenal biopsy, even in the presence of all of the four criteria mentioned above.

11 Do anti-gliadin antibodies still have an indication?

Antibodies aimed against native gliadin (AGA) no longer have an indication for celiac disease because their sensitivity and specificity has shown to be far lower than that of anti-tTG and EMA. AGA antibodies also lost the niche indication with regard to their use to identify celiac disease in early childhood, as they were replaced by anti-DGP antibodies in this clinical setting. One of the reasons that led the scientific community to renounce this test is its lack of specificity, as AGA is found in many other intestinal diseases and even in a non-negligible percentage of healthy controls. Albeit with limitations, the finding of AGA can be useful to support the suspicion of non-celiac gluten sensitivity in patients with intestinal and extraintestinal symptoms triggered by the ingestion of gluten and wheat. In these subjects, if positive on a diet containing gluten, AGA are negativised in parallel with the resolution of symptoms after the elimination of gluten from the diet. However, a patient should never be put on a gluten-free diet without first excluding celiac disease.

COMPLICATIONS

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1 What are the complications of celiac disease?

The most frequent complications of celiac disease are refractory celiac disease (type 1 and a type 2), ulcerative jejuno-ileitis, enteropathy T-cell type 1 (EATL) lymphoma, intra-abdominal B cell lymphoma, and carcinoma of the small intestine. Other more rare complications, if not anecdotal, are collagenous sprue and pharyngo-esophageal carcinoma.

In particular, refractory celiac disease either means the lack of clinical and histological response to at least 12-15 months of a rigorous gluten-free diet or the reappearance of villous atrophy, despite the fact that the gluten-free diet has always been strictly followed. The histological finding of an aberrant lymphocytic population and/or monoclonal gene rearrangements leads to a diagnosis of type 2 refractory celiac disease, a condition that can be considered pre-malignant as it often degenerates into EATL. Ulcerative jejuno-ileitis is a condition characterised by inflammatory ulcers affecting the small intestine that can either cause intestinal obstruction or become a breeding ground of lymphoma.

2 How often do complications of celiac disease occur?

Fortunately, complications of celiac disease are rare. A recent multicentre Italian study has shown that the annual incidence of complications in patients with celiac disease is approximately 0.2%. However, the same study also showed that the risk of developing these complications varies in different types of patients. Numerous studies have demonstrated the fundamental importance of maintaining a rigorous gluten-free diet, both in reducing complications and the mortality of patients with celiac disease. It has also been shown that the risk of complications is minimal, if not non-existent, in patients diagnosed before age of 40 years, and for mild symptoms, while it becomes very significant in patients diagnosed at a later age and with symptoms of severe malabsorption. On the other hand, even if these complications tend to arise soon after the diagnosis of celiac disease, patients with celiac disease can always potentially develop complications.

3 Why are the complications of celiac disease significant?

Numerous studies have shown that celiac disease is a condition with a double mortality compared to that of the general population. This excess of mortality is precisely due to the pre-malignant and malign complications of celiac disease. More specifically, 5-year survival is between 80% and 96% in patients with type 1 refractory celiac disease, but is only between 40% and 58% in patients with type 2 refractory celiac disease. This drops between 8% and 20% in patients with refractory celiac disease who develop EATL.

4 Which celiac patients are at greater risk of developing such complications?

It should always be remembered that patients at an increased risk of developing complications are those who do not follow a strict gluten-free diet. In patients who follow a strict gluten-free diet, however, the risk is higher in patients diagnosed after the age of 40 years and for those with symptoms of major malabsorption, i.e. diarrhoea, steatorrhea, and weight loss. The development of complications in patients diagnosed without symptoms or with minor symptoms it is instead much more rare, if not exceptional or anecdotal. It is therefore reasonable to think that the follow-up methods of these patients should be different. Patients with low risk of complications could be followed up only clinically; patients at high risk should be monitored every 6, 12 months with a clinical evaluation and blood biochemistry examinations such as blood count, inflammatory markers (including faecal calprotectin) and albuminemia, regardless of the clinical picture.

5 When should I suspect that a patient with celiac disease is developing a complication?

In patients with celiac disease, the onset of complications should be suspected when the clinical picture does not respond to a gluten-free diet or when symptoms of major malabsorption reappear (diarrhoea, steatorrhea, weight loss), anaemia, or increased inflammatory markers occur despite the patient is still following a strict gluten-free diet. In addition, the suspicion of complications must also arise in case of symptoms such as abdominal pain, fever, and bleeding. These symptoms are not typical of celiac disease; their presence at the time of diagnosis or their subsequent appearance should be considered with great care, and must lead to the suspicion of complications.

6 What tests are useful in patients with suspected complicated celiac disease?

If a complication is suspected, the patient should be sent to a reference centre where he/she can be examined in depth and exhaustively. The starting point is certainly that of a gastroscopy with multiple duodenal biopsies. If the biopsies show atrophy of the villi, a search for aberrant intraepithelial lymphocyte populations and/or monoclonal gene rearrangements must be performed. The endoscopic videocapsule is an essential test to adequately study the entire small intestine, and provides preliminary indications for the execution of a potential double-balloon enteroscopy. As abdominal B-cell lymphoma and carcinoma of the small intestine are potential complications, intra-abdominal complications in a broad sense that do not arise in the mucosa of the small intestine in these patients will always require a colonoscopy, CT (or RM) abdominal and PET.

7 What treatments are available for complications of celiac disease?

The treatment of complications of celiac disease varies based on the complication. Patients with type 1 refractory celiac disease are preferentially treated with steroidal immunosuppressive medication, primarily budesonide. Preliminary but promising results have been obtained with treatments based on mesenchymal cell infusions. Also type 2 refractory celiac disease can also be treated with budesonide or

systemic steroids but the results are much less satisfactory. The steroid treatment, coupled when necessary with surgical stricturoplasty of the intestinal strictures is the therapy of choice for ulcerative digiunoileitis.

The treatment of the EATL is definitely the most challenging one. Standard CHOP-based chemotherapy treatments have certainly been the most used, but the results are disappointing. Surgical debulking followed by chemotherapy and high-dose chemotherapy followed by autologous stem cell transplantation yielded better results, but in a very small number of patients. These treatments are so aggressive that very few patients can be candidates for this type of therapy when diagnosed with EATL.

THE TRANSITION OF ADOLESCENTS WITH CELIAC DISEASE FROM PEDIATRIC TO ADULT CARE.

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1 Who coordinates the transition?

The centre that formalised the diagnosis must coordinate the transition with a written report containing the information on the patient, with particular attention to the criteria adopted for diagnosis (e.g. diagnosis with or without intestinal biopsy), to the compliance of the gluten-free diet (e.g. good or bad adherence to diet therapy), to the clinical and biological effects derived from the gluten-free diet (such as the absence of symptoms referable to the proper execution of the diet, and the serum anti-transglutaminase antibodies concentrations in the course of gluten free diet), to the presence and management of associated diseases (such as type 1 diabetes mellitus).

2 Who monitors the adolescent or young patient with celiac disease?

The transition will always be agreed upon with the patient and his/her family if the patient is an adolescent (14-17 years of age). The referring physician may be the general practitioner with experience in the diagnosis and follow-up of celiac disease, or the gastroenterologist of the adult.

3 How is the transition organised?

The transition of the adolescent or young adult with celiac disease should include contact with a (see point 2) and the organisation of the initial visit by the paediatrician (or person treating the adolescent). Where possible, the first visit should be in the same clinic with the paediatrician, general practitioner and the patient. At least for the first year after the transition, and only at the request of the patient, the paediatrician (or the physician who monitored the adolescent) should offer his/her readiness to re-examine the patient.

4 Does the adolescent or young adult making the transition really have celiac disease?

As in point 1, we remember that a report should always be prepared on how the diagnosis was formalised: have the guidelines been respected? Has an endoscopy and histological examination of the intestinal biopsy been performed? And if not, why? If biopsy was performed, what degree of a histological lesion was found? Was it compatible with the diagnosis of celiac disease? It is important to re-evaluate the diagnosis with intestinal biopsy and after exposure to gluten:

- if the diagnostic guidelines have not been respected;
- if the adolescent has restarted a diet containing gluten and, having no symptoms, has independently questioned the diagnosis.

5 What should be evaluated during the interview with the adolescent?

- his/her autonomy in the management of the diet and knowledge about celiac disease;
- awareness of the risks involved in not following a gluten-free diet;
- the concept of contamination (e.g. the concept is too rigid thus there is a reduction in social life, or vice versa, frequently "cheats" without being aware of the risks involved?);
- true adherence to the gluten-free diet can also be assessed with interview questionnaires (ad hoc questionnaires) or with personal diet journals to evaluate true adherence to the gluten-free diet in the presence or absence of parents.

GLUTEN-FREE DIET AND PATIENT MONITORING

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1 What foods should be avoided in a gluten-free diet?

- Wheat, barley, rye, spelt, einkorn, khorasan wheat (usually marketed as Kamut®), spelled, triticale.
- Products based on and/or containing prohibited grains and flours, starches, groats, meal, creams, flakes, bran, and malt of prohibited grains.
- Oats (except that present as an ingredient in products on the National Register of the Ministry of Health).
- Other foods, such as beverages with prohibited grains, breaded or floured products or products mixed with breadcrumbs.

For further information, view the "ABCs of the celiac diet" at www.celiachia.it.

2 What foods are permitted in a gluten-free diet?

- Corn, rice, millet, buckwheat, quinoa, amaranth, teff, sorghum, potatoes, cassava.
- Substitute products present in the National Register of the Ministry of Health.
- Meat, fish, eggs, raw ham, milk, cheese, natural yoghurt, cream, vegetables, legumes, mushrooms, fruit, coffee, tea, wine, honey, sugar, butter, vegetable oils.
- Products considered "at risk" (such as flour, starches and permitted grain starches, ice cream, jams, sauces) that bear the label "gluten-free" on the label.

For further information, view the "ABCs of the celiac diet" at www.celiachia.it.

3 What nutritional precautions should be followed for proper gluten-free nutrition?

The gluten-free diet must be varied and balanced, integrating processed, gluten-free products. The nutritional needs of patients with celiac disease do not differ from those of a healthy subject (a balanced diet according to the needs for age groups. LARN 2014). It is not necessary to take supplements of particular nutrients if a varied and balanced gluten-free diet is followed.

4 What other precautions should be followed?

The AIC has issued a document on gluten contamination, which can be useful, and has a project on eating out while gluten-free. It is advisable to maintain a balanced approach towards the patient, especially in the most sensitive age groups such as adolescence. In addition to a correct selection of foods, it is also necessary to exclude small amounts of gluten from the diet that may be present due to so-called "accidental contamination". In addition to knowing the types of food that may contain gluten and for which it is necessary to check the label, it is therefore important for patients with celiac disease to pay attention when preparing food in the kitchen, by following a few simple rules, and choosing meals outside of the home. Patients with celiac disease can take all medicines on the market if necessary, even if they contain wheat starch as an excipient.

5 After the diagnosis of celiac disease, what control tests should be prescribed to patients with celiac disease and how often?

Upon diagnosis, it is important to provide education on the gluten-free diet by an expert dietician, and that the communication is adequate for the age, cultural and social habits of the patient. Continuous support over time promotes adherence to the gluten-free diet.

A check within 6-12 months from diagnosis and every 1-2 years thereafter (unless there are complications) is sufficient to verify compliance with the gluten-free diet, to verify the appearance of autoimmune diseases and/or metabolic alterations (which may also occur in treated patients with celiac disease) and the early diagnosis of complications.

At each control, patients with celiac disease should be subjected to a medical examination, dietary assessment, blood count control, IgA class assay of antitransglutaminase serum antibodies (or IgG if an IgA deficiency is present) and TSH. Other instrumental and specialist examinations, such as anti-TPOs, should be performed if the clinical evaluation recommends it. In adults, bone densitometry should be performed routinely at least once, and repeated if necessary.

6 What should be done if the patient has other associated diseases?

A balanced gluten-free diet should always be maintained. If necessary, medication prescribed for the associated disease must be taken, and examinations required for follow-up must be performed. For patients with celiac disease and type 1 diabetes (the prevalence of celiac disease is 5-10% among patients with type 1 diabetes) be aware of the glycemic index of foods, also by making meals rich in fibre or grains that are naturally without wheat gluten, where possible.

AUTOIMMUNITY AND CELIAC DISEASE

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1 Is celiac disease an autoimmune disease?

Celiac disease is now considered by most of the researchers to be an autoimmune disease, albeit with peculiar characteristics. The strongest evidence in favour of its autoimmune nature is the presence of autoantibodies in the serum of patients. In reality, anti-tTG antibodies, which are so important in the diagnosis of the disease due to their high sensitivity and specificity, are not the only antibodies. Anti-actin antibodies are also present, which have also found space in diagnostics as they are mostly elevated in patients with severe mucosal damage, as well as anti-Purkinje, anti-calreticulin, anti-zonulin, anti-ganglioside, anti-enolase and others. The second line of proof is the association of celiac disease with other clinical conditions that are unquestionably that of autoimmune pathogenesis (see below). Lastly, in favour of its autoimmune nature, the association with genes common to other autoimmune conditions and the sharing of pathogenetic mechanisms with these, mainly with type 1 diabetes. The peculiarity of celiac disease in the field of autoimmune diseases, which makes this a unique model for the study of autoimmunity, is the clear role played by gluten as a triggering factor, and more importantly, the reversibility of the autoimmune process and the possibility of "turning it off" with the elimination of gluten from the diet.

2 What is the role of gluten in triggering autoimmunity?

Certainly anti-tTG antibodies, but also other autoantibodies (anti-actin, anti-Purkinje) are gluten-dependent, and in other words tend to disappear with the elimination of gluten from the diet. It is also interesting to note that T-specific cells have not been shown to play a role. The most accepted current hypothesis to explain the gluten-dependency of the production of anti-tTG antibodies is that tTG-gliadin complexes are recognised and processed by B-tTG-specific cells, which then receive the necessary signal for the production of anti-tTG antibodies from gliadin-specific T cells. In-vitro studies suggest the ability of gliadin peptides to activate the production of type 1 interferons, molecules involved in protection against viral infections as well as the activation of autoimmunity. Similarly to that hypothesised for type 1 diabetes, viruses have also been implicated in the process that leads to the activation of autoimmunity. There is evidence of anti-rotavirus, and more recently, anti-reovirus responses that are higher in patients with celiac disease compared to control subjects. Clinical studies have not yet fully shed light on the relationship between the duration of gluten exposure and the risk of developing other autoimmune diseases. It remains to be seen whether the established association with the former is linked to an active role of gluten in promoting autoimmunity in general, or to the simple sharing of genes that make it susceptible to the development of autoimmune processes.

3 What are the clinical presentations referable to autoimmunity, and which autoimmune diseases are associated with celiac disease

Celiac disease is characterised by proteiform clinical manifestations, from the classic malabsorption syndrome to extraintestinal manifestations. For the first, the pathogenesis is certainly linked to serious mucosal damage that, limiting the surface of the intestine, also limits the absorption of nutrients with the consequent development of syndromes due to deficiency. However, there are other clinical manifestations that do not appear immediately justified by malabsorption. A few examples of these are articular manifestations, those neurological, and myocardiopathies. Autoimmune mechanisms have been hypothesised for these. These may involve the same anti-tTG antibodies that have been shown to deposit themselves in tissues, including nervous tissues, as well as other autoantibodies such as those towards Purkinje cells, which are potentially responsible for the ataxic symptomatology displayed by some patients with celiac disease. In this context, the presence of autoantibodies specific to the type of clinical manifestation should be noted, such as the increase of anti-tTG 6 antibodies in patients with neurological manifestations and that of anti-tTG 3 antibodies in patients with ED.

As regards autoimmune diseases associated with celiac disease, many of these are endocrinopathies, first of all of type 1 diabetes mellitus, Hashimoto thyroiditis and Addison's disease. There is also an association with Sjogren's syndrome, psoriasis, rheumatoid arthritis, autoimmune hepatitis, sclerosing cholangitis, and alopecia areata.

4 How is the diagnosis of celiac disease managed in children with type 1 diabetes?

The association between celiac disease and type 1 diabetes is the most documented and studied. Recent meta-analyses that have considered up to 11,000 cases of type 1 diabetes indicate that the prevalence of celiac disease is approximately 3-7%. The opportunity to screen these patients for celiac disease has much been debated; today most scientific societies recommend this procedure made effective by the high sensitivity and specificity of serological tests, in particular the anti-tTG IgA assay. The ESPGHAN guidelines for asymptomatic cases (most of which are those with type 1 diabetes) provide the first step in HLA typing to identify those at risk and monitor them over time. A series of papers published in recent years have deemed this practice to be unnecessarily expensive, as the majority of diabetic patients are HLA-DQ2 or DQ8-positive. There remains a need to subject them to total IgA and anti-tTG IgA assays. An additional problem may be represented by subjects with only marginally elevated titres of these antibodies. To tell them apart from "false positives", it is also useful to have confirmation of the positivity of EMAs, which are known to have a greater specificity for the diagnosis of celiac disease. However, their positivity implies the performance of an intestinal biopsy. One last point still in discussion is the screening frequency (how often patients are tested) and for how long this procedure should be performed. In this regard, data from the literature indicate that 80% become serum-positive within the first 5 years of diagnosis of type 1 diabetes, and only 5% are expected to develop auto-antibodies after the tenth year.

5 Should the gluten-free diet be introduced in cases of autoimmune disease affected by “silent” celiac disease, and what is the effect of the gluten-free diet on the associated autoimmune disease?

The discussion about whether or not to undergo celiac disease screening for people with type 1 diabetes focuses mainly on the benefits that can be derived from the establishment of a gluten-free diet. As already mentioned, many of the patients that tested positive for celiac disease are asymptomatic. However, recent prospective and randomised studies have shown an unquestionable benefit not only on intestinal histology, but also as regards other parameters such as the perception of health and psychological well-being. Objectively, a significant improvement in nutritional status is seen in subjects that are seemingly asymptomatic. Probably the most important aspect is that of the protection of bone health. Subjects with diabetes and celiac disease that is not treated with diet have a much lower bone density than those who follow a gluten-free diet. This all leads to prescribe the gluten-free diet in subjects in whom intestinal mucosal atrophy has been documented, even if they are asymptomatic. Prospective randomised studies continue, from which it is hoped to obtain stronger and more definitive evidence. The behaviour to follow in the event of potential celiac disease is still uncertain (serologically positive subjects, but with normal intestinal mucosa): see the previous sections for more information on this topic.

While a gluten-free diet seems to have a significant benefit on growth and nutritional status, it appears to have little impact on the management of diabetes. This is common to other autoimmune diseases (thyroiditis, hepatitis), in which, once organ damage has been established, it is not reversible with the elimination diet.

PSYCHOLOGICAL ASPECTS

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1 Why do I always feel tired, even in the morning?

Asthenia, more commonly reported by patients as fatigue, is common in celiac disease, both before starting the diet and sometimes afterwards, even if less intense and frequent. The causes are unknown, but the feeling of general malaise when celiac disease is not yet diagnosed, or the progressive reduction of physical activity, vitamin and mineral deficiencies and even a widespread depressive state can all be contributing factors to asthenia. There are few studies that say what the most effective treatment is in these cases. In clinical practice, however, a good gluten-free diet, and even progressive physical training (starting with a few minutes of exercise or a short walk per day) can be of assistance.

2 Why do I not sleep well?

Sleep disorders are common in all chronic diseases, and celiac disease is no exception. Sleep disorders prior to diagnosis are related to general malaise, body and muscle pain, and altered mood states (anxiety, depression). Unfortunately, sleep disorders may persist in adults, likely also due to the altered biorhythm acquired before diagnosis. To improve the quality of sleep, the advice to provide is that for any insomnia: light meals that are not too close to bedtime, little computer and mobile phone use in the two hours before bedtime, little TV if it tends to keep the patient awake, herbal tea or relaxation techniques of the body and mind.

3 Why do I feel a sense of anger if I think about the limitations that celiac disease imposes on me?

The diagnosis of celiac disease changes the lives of patients. Although the benefits are clear and obvious to everyone; if the availability of good gluten-free food makes the diet less of a chore, the limitation cannot be denied. For someone who travels and eats out often for work, for example, or for those who cook for all of the other members of the family, more often women, it is a question of resisting temptation on a daily basis. In short, this is generally a normal reaction. If the anger is controlled and minimally affects the quality of life, it will diminish with the continuation of the gluten-free diet and adapting to a new life. If this does not happen, it is best to recommend psychological counselling.

4 I know I shouldn't, but it happens to me, why do I cheat while on the diet

Unlike food allergies, celiac disease may not cause immediate and severe symptoms upon ingesting gluten. This is why patients are subject to gluten-free diets, especially if they are young and asymptomatic or with mild or few symptoms when diagnosed, they tend to occasionally ingest small amounts of gluten because apparently "nothing happens" immediately. In reality, although one single intake of gluten does not trigger any symptoms, the repetition of cheating leads to a reappearance of intestinal damage and

presence of the specific antibodies in blood, such as to void all of the sacrifices that the patient has made up until then, in addition to increasing the risk of developing complications.

5 I'm afraid to eat at restaurants because my food could be contaminated, is there reason to worry?

Fear is justified because we are surrounded by gluten, however, thanks to informational campaigns and the increased awareness about celiac disease by the food service industry, the risks of contamination tend to be null. It would be absolutely wrong to avoid going out and social relationships because of celiac disease, as this would result in psychological repercussions that must be avoided. If the patient follows a strict diet at home and always communicates that he/she has celiac disease at restaurants and uses products that are "naturally gluten-free", eating out at a restaurant can be enjoyed.

6 I'm afraid of having health problems because I have celiac disease, is it justified to be concerned?

When diagnosed, patients with celiac disease can present a wide variety of gastroenterological symptoms/signs such as disorders of the abdomen and abdominal and non-gastroenterological pains such as anaemia and osteopenia, which tend to improve until they disappear with the beginning of a gluten-free diet. However, there are associated autoimmune diseases such as Hashimoto's thyroiditis, vitiligo or type 1 diabetes, that are not much influenced by the diet and which may also be diagnosed subsequently to the exclusion of gluten. The most feared and rare neoplastic complications are intestinal lymphoma and jejunal carcinoma, which usually appear near the time of diagnosis, but careful follow-up allows for early diagnosis. The gluten-free diet is currently the only treatment of celiac disease and the only way to avoid its associated complications; the patient must only follow a proper diet and have follow-ups within the required time frame.

7 I often feel unmotivated and like I've slowed down, my doctor says I'm depressed. What is the relationship between depression and celiac disease?

Depression is associated with celiac disease and tends to persist -even if to a lesser extent - even with a gluten-free diet, and may also affect adherence to the diet. If depression is present, psychological support should be recommended. The causes of depression before diagnosis may be the often unexplained feeling of chronic malaise, but also vitamin deficiencies and autoimmune diseases associated with celiac disease; diet-related limitations may be due to its persistence in the post-diagnosis period.

8 I think that I won't be able to have a normal life because of my illness. Is this true?

Well-treated celiac disease and above all, diagnosed early, allows for a normal life in all respects. Some scientific information, especially in the past, about the possibility of developing atumour or disabling diseases have now been reviewed in light of new epidemiological data on the disease. Today, collaborative studies performed in Italy tell us that the frequency of complications is rather rare.

9 Am I wrong to think that there are no alternative therapies to a gluten-free diet?

To date, an alternative therapy to a gluten-free diet is objectively rather far off. For some patients, this may be a reason for depression, or lack of confidence in the future. We must always think that a gluten-free diet is a perfect treatment, without side effects. It is difficult to find a medication that is just as effective. However, research is advancing at an international level, and alternative strategies for the diet-based treatment are being studied.

10 Is it wrong to think that it is difficult to travel or take long trips because of my illness?

It is incorrect to think that long journeys are too difficult to plan. Of course, a minimum level of organisation pre-departure is necessary. The internet helps a lot, and the existence of patient associations such as the AIC in many other countries can be a valuable resource. In today's day and age, cruises and tour operators, hotels, and tourist villages offer the choice of gluten-free meals even during the booking phase.

REGULATORY ASPECTS

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1 What is the difference between the claim “gluten-free - suitable for celiacs” and “gluten-free - specially formulated for celiacs”?

The word gluten-free is a voluntary nutritional claim that is present on the label of industrially processed foods for which the producer guarantees a gluten content of less than 20 ppm (or mg/kg). The gluten-free claim cannot be used for foods that are naturally gluten-free, sold as such without having undergone industrial processing. The gluten-free claim must be followed, as required by Reg. EC 828/2014, by the words “- suitable for celiacs” if it is a food product that avoids contamination with food production chains containing gluten and/or that avoids the addition of additives containing gluten. The wording “- specially formulated for celiacs” is followed by the gluten-free claim on the label of substitutes for foods whose predominant or sole ingredient is grain that contains gluten, which were produced using grain that is naturally gluten-free or deglutinated grain.

2 What is the monthly free supply of gluten-free products specially formulated for celiacs? How do you get it?

Every person affected by celiac disease has the right to receive an exemption, whose amount varies according to age and sex, for the purchase of gluten-free products specially formulated for celiacs that are named in the National Food Registry. To have the exemption, after receiving the diagnosis at a Network Office or Centre of Reference for the diagnosis of celiac disease in the Region of residence, the person with celiac disease must go to the regional health authority with documentation certifying the diagnosis. The regional health authority then gives celiacs 12 monthly vouchers (in paper or electronic format, depending on the regional organisation) for the purchase of food products specially formulated for celiacs, corresponding to the sum to which he/she is entitled. The coupons for the exemption, at their time of going to press, can be used in all the marketing channels for gluten-free products (pharmaceutical, parapharmaceutical, specialised shops and large-scale retail stores) only in some Regions and Autonomous Provinces; in those where this is not permitted, the only channel where the exemption can be used is the pharmaceutical channel.

3 What are Essential Assistance Levels? Why do they also affect celiac disease?

Title V of the Constitution states that health is the subject of concurrent legislation by the Regions and Autonomous Provinces. The Essential Assistance Levels (ELA) are the diagnostic and therapeutic services that every Regional Health Service is obliged to provide, regardless of its legislative autonomy in the field. The provision of a service on the list of ELAs is not necessarily free, but can also take place upon payment of a portion of the cost by the citizen, called a ticket. The ELAs represent a minimum list, the Regions and

PA (if they are not returning from deficit) can integrate this list with additional services or identify methods of the provision of benefits that are better for the client than those envisaged by the ELA, using its own financial and structural resources. The ELAs concern celiac disease, as this condition is present in the list of chronic diseases, which automatically involves the presence of all examinations scheduled for follow-up and monitoring in the ELA. The diagnosis of celiac disease is also protected by the ELA, as diagnostic tests (anti-tTG and EmA assay, the genetic test for DQ2/8 and duodenal biopsy) are included in the list of outpatient diagnostics.

4 Are public canteens obliged to supply gluten-free meals to those who request it? Is it a free service?

Article 4, paragraph 3 of Law 123/2005 establishes the right for people with celiac disease to receive gluten-free meals in public, school and hospital canteens, whenever they request it. This service is free, as nothing more is due from the person with celiac disease compared to the cost of the corresponding meal with gluten. Gluten-free meals can be composed of foods that are naturally gluten-free and/or packaged products labelled "gluten-free"; however, in must have a gluten content of less than 20 ppm (or mg/kg). Article 4, paragraph 4 of the aforementioned Law 123/2005 provides that the Regions and APs (Autonomous Provinces) annually receive funds for structural changes to public canteens, so that they are made suitable for the preparation and delivery of gluten-free meals as well as for training staff who work in public canteens on how to safely provide gluten-free meals. The Report to Parliament on celiac disease contains the number and geographical distribution of public, school and hospital canteens in Italy.

5 Can products labelled "low in gluten" be eaten by celiacs?

European Regulation 828/2014 (Annex A) provides that the term "gluten-free" is only permitted where the gluten content of the food sold to the final consumer does not exceed 20 ppm or mg/kg, and that the words "with very low gluten content" is allowed only where the gluten content of the food sold to the final consumer does not exceed 100 mg/kg. The gluten-free diet includes the use of naturally gluten-free products or those with the wording "gluten-free," which therefore ensure a gluten concentration of less than 20 mg/kg. Foods with very low gluten content are difficult to find in Italy, there is no indication to promote their consumption at the expense of gluten-free products, as they are products neither new in type, nor more palatable, nor cheaper. They are not in themselves forbidden to celiacs, who should however consume them in smaller quantities than the equivalent "gluten-free" products.

FRONTIERS OF RESEARCH

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1 Considering the results of scientific research over the last decade, is it still relevant to talk about alternative therapies to a gluten-free diet?

Research has certainly made great strides in the last ten years as regards the understanding of mechanisms of lesions triggered by gluten in people with celiac disease. The more we seek to understand how gluten triggers inflammation in the intestinal mucosa, the greater the chances of intervening and blocking this process become. One could say that they nearly go hand in hand. While basic researchers identify and put together the various pieces of the complex inflammatory mechanism, other scientists (sometimes even the same ones) study the best way to antagonise every single injurious process in the laboratory. A few examples: we know that the high content of two amino acids, glutamine and proline, gives gluten proteins a remarkable resistance to digestion by gastro-intestinal juices, with the release of large fragments with high inflammatory potential at the level of the intestinal mucosa. We know the nature of these fragments and the way that they cross the intestinal barrier, and how these peptides are modified by the tissue transglutaminase (tTG) enzyme, which is particularly abundant in the intestinal mucosa of celiacs. Overall, scientists have put together the various pieces of the complicated mosaic of celiac disease, which has made the development of more than 15 different drug therapies possible to date, some of which are already nearing clinical trials.

2 What characteristics must a pharmacological therapy have to replace the gluten-free diet in a safe and effective way?

The gluten-free diet is currently the only therapy available for the treatment of celiac disease. It is safe, has no side effects on the general health of the patient, and allows restoration of the normal morphology and function of the intestine. However, even after many years of a scrupulous diet, gluten tolerance is not re-gained, and the symptoms reappear almost immediately with the reintroduction of gluten in the diet. It is intuitive that a new drug should guarantee an efficacy of treatment and safety that is comparable to the gluten-free diet. An alternative therapy should protect patients from the daily and prolonged intake of foods based on prohibited cereal flours, which are part of a regular diet. There are still many questions to be answered, which mainly concern: 1) the maximum amount of gluten per meal that can be eaten during each treatment, and 2) the duration of protection to the gluten containing diet. To date, many research groups are setting the primary objective of developing medications capable of providing protection for accidental or occasional gluten exposure. This would naturally already be a big step forward.

3 At what point is the research on pharmacological therapy, the so-called “pills”?

As regards pharmacological treatments for celiac disease to be taken orally (the so-called pill), there are currently several being studied. A treatment pill was discussed in Italy for the first time in 2005, at the international conference organised by AIC. It is a small molecule, developed by Alessio Fasano of Harvard University, which would prevent the passage of gluten in the intestinal mucosa, block the opening of the intestinal canals, and hence block the trigger of the immune reaction. The molecule (known as Larazotide or Larazotide INN-202) has also been tested for efficacy on volunteers with celiac disease in several clinical trials in the United States. While these studies have shown a total absence of toxicity and side effects (a prerequisite of each medication before evaluating its effectiveness), only a partial protective action was observed as regards gluten-induced damage. Another therapeutic frontier is represented by pills based on glutenases, enzymes that have a high efficacy in breaking down gluten proteins, in particular at acidic conditions of the first digestive tract.

4 What is the specific mechanism on which the protective action of glutenases is based?

As mentioned previously, one of the special features of gluten proteins is the remarkable resistance to digestion by gastro-intestinal juices. This involves the release of peptide fragments with high inflammatory potential in the first intestinal tract. Glutenases are proteolytic enzymes that preferentially cut the link between proline and glutamine, and therefore are highly effective in digesting gluten (hence the name glutenase or even prolylendopeptidase). Several pharmaceutical companies both in Europe and in the United States, are investing in producing glutenases from micro-organisms and that are very resistant to the highly acidic conditions of the stomach. Research centres in both the academic world and pharmaceutical companies have created experimental stomach and bowel models to reproduce gluten digestion conditions in the laboratory. These in-vitro studies have shown that glutenases, produced in some species of bacteria and fungi, can break down the amount of gluten contained in a hamburger bun in a few hours, which are extremely promising results.

5 If it becomes available, will the glutenase-based pill allow for complete tolerance or will it only offer partial protection, such as for accidental gluten contamination?

This is a key question, on which the therapeutic success of the new glutenase pills will depend. The current orientation of the scientific world is prudent, as to date researchers are working on a use of glutenases that guarantees safe protection against occasional and/or involuntary gluten intake, and does not completely replace the gluten-free diet. It should however be said that one of the greatest difficulties of celiacs is how to follow the safe diet when travelling or at social events. Having a therapy that allows total protection against the occasional ingestion of gluten would, in my opinion, be a huge step forward. The research team coordinated by Dr Robert Anderson of Boston, who formulated the vaccine for celiac disease, is working precisely on this, namely on preventing injuries from sporadic exposure to gluten, which is yet another promising strategy in the panorama of therapeutic alternatives.

6 What is the gluten-free vaccine based on? Where do clinical trial on patients currently stand?

It is a desensitising vaccine designed to induce tolerance, and therefore to induce harmless the pro-inflammatory T lymphocytes responsible for inflammation in celiac disease. Nexvax2, the name of the vaccine, is a molecule composed of three large fragments of gluten amongst those most immunologically active, and formulated for subcutaneous injections. The curative potential of the treatment lies precisely in the specific strategy of administration: in the skin and not orally. Researchers demonstrated that the administration of gluten peptides into the dermis activates regulatory cells that produce inhibitory substances (particularly IL-10), which block reactive T lymphocytes in the intestine. The vaccine successfully passed phase 1 of a clinical trial to verify the safety of the vaccine. Recently, the results of phase 2 of the trial, performed on Australian and Zelandese patients, have been made public. The maximum tolerated dose (0.150 mg of the medicine and two injections per week) and the duration (2 months) of treatment were determined, and neither symptoms nor particular damage to intestinal mucosa were observed. Pending further investigations, or the evaluation of the protective effect on gluten intake of both glutenase and the vaccine, there is a certain optimism in the scientific world on the possibility of soon having alternative therapies to the gluten-free diet, or even diets based on experimentally detoxified grains.

7 What is meant by detoxified grain, and what are the most scientifically promising detoxification strategies?

For Detoxified grain is intended the grain that, albeit not tolerated by celiacs (wheat, barley, and rye), undergoes enzymatic or biochemical processes in the laboratory that neutralise the immunological toxicity of gluten. The technological processes underlying detoxification concern the pre-treatment of the flour before it is ingested, and the research is strictly Italian. The research group coordinated by Prof Marco Gobetti, a microbiologist at the University of Bolzano, has developed a method based on the treatment of flour with a mixtures of lactobacilli and mushrooms which release proteolytic enzymes that digest gluten below the accepted threshold to be considered gluten-free. Pre-digested flours are already available for the gluten-free diet. The other technological approach, developed by Dr Mauro Rossi of the Italian National Research Council (CNR), is based on knowledge of the mechanism of action of tissue transglutaminase, a key enzyme in celiac disease. The innovative technology uses microbial transglutaminase and a modified amino acid, methylated lysine. Through a transamidation reaction, the ability of gluten to be recognised by T lymphocytes is blocked. Some clinical trials on celiac volunteers have shown the reduced toxicity of transamidated flour compared to control flours. Further confirmations are awaited in order to obtain the green label for food products for celiacs.

8 Would the availability of “detoxified” flours on the market allow those who suffer from celiac disease to have non-specific diet, or is it necessary to always consume controlled products based on treated flours?

Pre-treated flours are part of dietary products for celiacs, and are therefore in the context of an alimentary regimen based on dietetic foods. The availability of detoxified flours does not allow the at-will consumption of flour-based products that have not previously undergone a certified detoxification process, or that they are naturally gluten-free.

9 Are naturally detoxified grains suitable for the diet for celiacs?

If we talk about wheat, rye or barley, the answer is absolutely NO. There are no cultivars of these cereals that are naturally devoid of gluten proteins. However, there are species of grains which by their nature contain gluten with a reduced inflammatory capacity. Among these, einkorn (also known as little spelt) is gaining the interest of researchers. It is a grain that has very distant origins that date back 10,000 years ago, and has formed the basis of the diet of agricultural populations for thousands of years. Einkorn was then replaced largely by soft and durum wheat that was more productive and easy to thresh. Einkorn has a simpler genome than other grains, has good bread-making and pastification properties and is rich in micronutrients. Recent research coordinated by the undersigned and Dr Mamone of the CNR of Avellino, in Italy, have shown that this ancient wheat contains a gluten whose primary structure is more significantly broken down by digestive enzymes, and is consequently more digestible than durum wheat or soft wheat. Through a process that mimics gastrointestinal digestion followed by proteomic analysis and immune toxicity on lymphocytes of celiacs, it has been observed that the gluten peptides responsible for immunological toxicity are partly destroyed in einkorn during the digestion process.

10 Even if they are not safe for celiacs, can these ancient grains with more digestible gluten prevent celiac disease in individuals with a high genetic predisposition?

In the recent time, researchers have been interested not only in finding an alternative treatment to the gluten-free diet, but also in the prevention of celiac disease, especially in those who have a high risk of becoming ill, such as carriers of HLA risk genes and first-degree relatives of celiacs. There are still many unanswered questions to think about the prevention of celiac disease. First, it is not known what the gluten threshold is that induces the pathology. Second, is this threshold different in high-risk individuals than in the general population? If research can provide confident answers to these questions, it would be interesting to experiment if a diet with more digestible gluten, as eating ancient grains, can maintain the levels of immune activation below the threshold required to trigger the pathology in high risk subjects during years of gluten-containing diet.

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Federica Stufi, volleyball player in Serie A, celiac.

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