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Celiac disease: An epidemiological condition: Insight on gluten free diet, significance and regulatory recommendations

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Abstract
Celiac disease (CD) is a chronic small intestinal immune-mediated enteropathy due to exposure to dietary gluten in genetically vulnerable people. Enteropathy associated to the CD contributes to several macro- and micronutrient-related nutrient failures. Celiac disease remains underdiagnosed in several regions, which can result in severe health issues. Non-invasive and inexpensive ways, such as video capsule endoscopy, are currently used for the diagnosis of celiac disease. The aim of this paper is to safe cure for CD by excluding the gluten from the diet, and providing gluten free diet (GFD) according to regulatory recommendations. The diet must not only be free of gluten, but must also be nutritious in order to avoid nutrient, vitamin and mineral deficiency or excess. Hence, we included the GFD, DASH (Dietary Stop Hypertension Appropriations), balanced kidney diet, ketogenic diatribe and low-FODMAP (Fermentable Oligo-, Di-, Mono- saccharides and Polyols) diet, which are forms of medically trained diets. Latest analysis shows that both recently diagnosed and post-GFD CD patients also have nutritional deficiencies. The results of this study reveal the value of a nutritionally healthy diet plan as part of CD treatment. Since celiac disease is a chronic disorder with a variety of symptoms that can be successfully diagnosed and treated to avoid both acute and long-term consequences, it can educate regular clinical practise in all medical disciplines. Patients should live on a completely GFD. A healthy GFD should be focused on a mixture of naturally gluten-free foods and certified gluten-free processed items.

Keywords: Celiac disease, VCE, gluten free diet, DASH, nutritional deficiencies

Introduction
Celiac disease (CD) is characterised by mild intestinal disruption and malabsorption of nutrients [1]. In the last fifty years, tests of accumulated serum have demonstrated a 4-fold rise in CD incidence [2]. The spatial, north-south and west-east spread of CDs in Europe in combination with the socioeconomic condition and findings of population migration indicate a climatic effect that contributes to a rise in the occurrence of CDs, but this issue is much more discussed [3, 4]. We already recognize that a CD can not only contribute to minor intestinal inflammation at various stages but also to a broad spectrum of gastrointestinal and extra-intestinal events and even to asymptomatic individuals [5]. The most frequent signs of extra-interlineal disorder involve irregular enzymes such as arthralgia/arthritis, alopecia, fatigue, headache, anaemia and sores in the mouth, body aches, depression, rashes, neuropathy, short stature, delayed puberty, osteoporosis, and infertility. The celiac syndrome is a disorder influenced by gluten intolerance and affects individuals of all age groups. It is classified as autoimmune enteritis, which is characterized by the presence of transglutaminase two autoantibodies and the breakdown of the small intestine mucosa, followed by a variety of clinical results. Extra-intestinal signs are not recognised as clinically specific to the celiac condition; the disorder also is found in old aged people [6]. Even in unusual celiac disease cases, the correlations among gluten consumption and clinical effects have been seen [7]. The treatment is focused on a rigid gluten-free diet for individuals with celiac disease, and no major changes have occurred in the latest decades [8]. Gluten must also be completely omitted from the diets of oversensitive individuals. Once considered rare, Celiac disease is now appearing in several Asian countries; Asia is currently at the forefront of the celiac disease phase. In Parts of Asia, like India, Turkey, Israel, Saudi Arabia, and Iran, celiac disease is as common as in the great majority of the country Primary care doctors and clinicians need to become more informed of celiac disease.

Any of the unserved needs in Asia are the universal provision of serological testing, reliable gluten-free products, and gluten labelling laws, dietician preparation and the development of patient support groups [9]. Gluten is an insoluble water protein that includes rye, barley, and wheat. Tissue transglutaminase (TTG) antibodies can be found in many patients' serums. Diagnosis includes rigid adherence to a gluten-free diet and regular lifelong clinical checking [10]. In modern nutrition, around 10 thousand years ago, gluten-containing crops have been added, but since then, more wheat variants have been chosen for technical instead of food purposes. Due to its technological and organoleptic attributes, Gluten is among the food ingredients most widely used in the sector [11]. In recent years enhanced harmful impacts have been identified in the sense of wide exposures to gluten [12]. This research evaluates dietary and biochemical elements of GFD objectively, explains the essential features of GFD and CD gluten, stressing the particularities and impacts of the food in conformity.

Gluten: Origin, Structure, Sources

Stock proteins of wheat (*Triticum aestivum*) or certain grains, rye-like (Secale cereal) or barley (*Hordeum vulgare*), which contribute to the Poaceae genus, are gluten and gluten-related proteins. Gluten-related proteins may be called secalin and hordein for rye and barley, respectively. In barley, triticale, spelt, or kamut, proteins similar to gluten can also be identified [13]. The packaging sector has a crucial role in gluten and gluten-related proteins as they have viscosity, cohesiveness, elasticity and absorption of water for the bread of dough and various baked items. They are most significant for offering a wide range of products, including spaghetti, beef, ice cream, dressings and more, with consistency and unique organoleptic properties [13, 14]. The proteins in gluten and gluten are gliadins and glutenins. Gliadins are proteins of prolamin, and ethanol dissolves. Gliadins are proteins of gluteal and soluble in poor acid solutions. Gliadins and glutenins characterise a higher degree of genetic polymorphism. The amount and form of protein vary with the hereditary character of wheat and other gluten-containing seeds and environmental influences [13]. In the responsive and rheological composition of various wheat types, both gliadin and glutenine proportions have equivalent meaning [15]. Gliadins and Glutenins enhance the amino acids glutamine and proline. Glutenins are protein polymers linked by disulfides, the subunits of the High Molecular-World Subunit (HMW) and the low Molecular-World Subunit (LMW). The disulfide bonding is necessary to hold a gluten protein framework and shape to offer its unique pliered structure after protein synthesis. Intrachain disulfide bonds are necessary for gliadin & Intra/interchain disulfide bonds are necessary for LMW and HMW. Figure 1 shows structure of gluten.

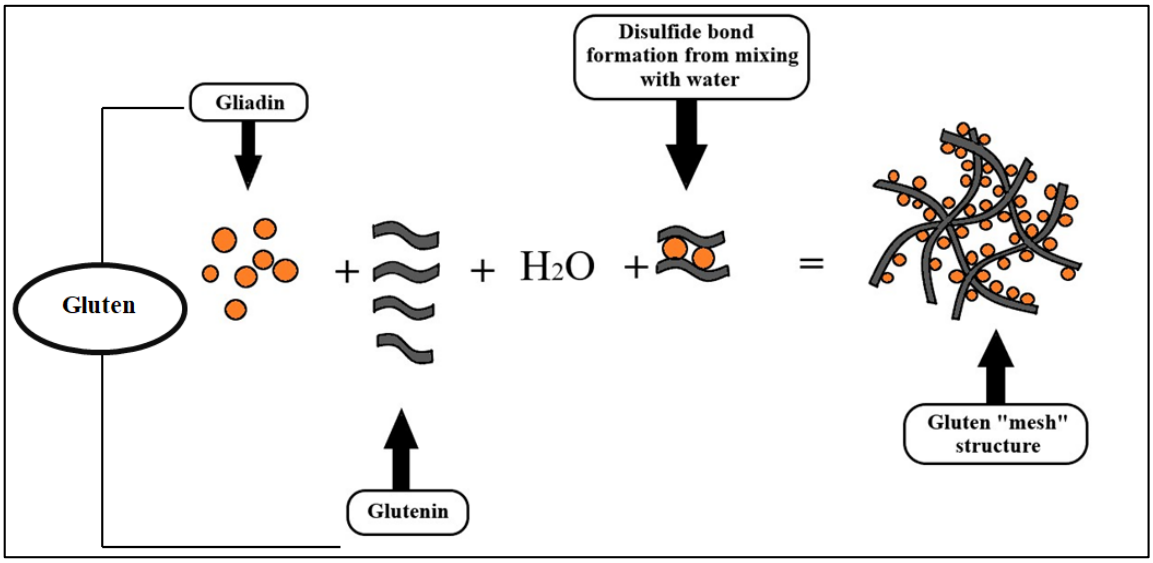

Fig 1: Structure of gluten

Gluten-Free Diet

A balanced diet leads to defending against hunger due to nutrition and excess nutrition, as per the World Health Organization (WHO). A balanced diet also prevents non-communicable disorders (NCDs) such as diabetes, heart and strokes, a significant public health problem and challenge on Western health systems. As illustrated in most global nutritional recommendations, the main attribute for a healthy diet is diverse and balanced. It should be higher in fruits and vegetables and low in processed grains, as well as low-fat or non-fat dairy products, fish, legumes, and nuts. This should ensure a higher consumption of dietary fiber (DF) and polyunsaturated fatty acids and lower oil, sugar, salt & saturated fatty acids. Allergies and intolerances of foods and some medical disorders necessitate 'special diets' for healthier people. The gluten-free diet, DASH (Dietary Approaches to Stop Hypertension), balanced kidney diets, ketogenic diets, and low FODMAP (Fermentable Oligo-, Di-, Mono-saccharides And Polyols) diets are examples of the diet which was used for medicinal purposes. These diets restrict or exclude specific food ingredients or types that could cause an allergy or aversion or be dangerous to other people. To achieve a diet that contains a gluten-free diet (GFD), gluten is completely excluded, a protein complex found in food items from wheat, rye, barley, oats, spelt, kamut or its varieties. This only includes foods that are naturally gluten-free (GF), e.g. legumes, fruit and vegetables, meats, seafood, eggs and dairy items, or alternatives to foodstuffs that are made from wheat that are specifically made for gluten or have a gluten level below 20 ppm, as described by the European legislation [16]. GFD therapy is needed under three situations: allergy to wheat, non-coeliac gluten sensitivity and celiac disease (CD). Wheat allergy is an immune response to wheat proteins that is more frequent in children. The non-coeliac gluten intolerance

is a condition that occurs when people consume the above-mentioned cereal proteins, with symptoms improving when they are eliminated from their diet [17]. While CD is a recurrent, small-intestinal immune-mediated enteropathy distinguished by particular antibody towards tissue transglutaminase 2 (anti-TG2), endomysium & deamidated peptide gliadin, which affects 1 in every 100 people in the western society [18]. Long-term CD-related complications, including lymphoma, osteoporosis & anaemia, were recorded. Rigid adherence to GFD and long-term removal of gluten from the food is the first medication and probably the most reliable CD medication. While narratively clear, compliance with the GFD is complicated because of its effect on the quality of life; this varies on environmental and individual considerations. The affordability, value for money, and effective labeling of GF foods are key factors impacting dietary enforcement. The supply of GF food items has increased considerably over the last five years: GF foods can be bought in large retailers, health food outlets and internet shops **[16]**; moreover, they are substantially quite costly than gluten-containing foodstuffs [19, 20]. As a part of certain grains, gluten is not usually described specifically on the package insert, so it can be hard to distinguish foods that contain gluten. It may also be available as a hidden food portion. Its analytical qualities are utilized as a flavor additive, thickener, emulsifier, filler, and fortifier and can be hidden under the words "flavourings" or "hydrolyzed vegetable proteins." Dysfunction in CD individuals' social recreation habits has also been noted [21]. This paper aims to examine the nutritional content of gluten-free items accessible in the marketplace and analyze the potential relationship of gluten-free products to the nutritional condition of celiac sufferers on GFD. The report then describes the nutritional deficiencies in the CD treatment and GFD conformity. This is followed by an exploration of GF wheat replacements' nutritional structure, which is presently accessible; it is the most recurring, from food analyses carried out over the last five years.

Epidemiology of celiac disease: Previously believed to be occurring only (or predominantly) in northern and Western Europe, celiac disease is presently globally identified. A systematic analysis of the global prevalence of celiac disease showed a seroprevalence level of 1.4%, with prevalence ranging across the world from 1.3% (South America, 11 surveys) to 1.8% (Asia, 20 surveys) **[22]**. Celiac disease is a widespread disease affecting both adults and children. While the average age at diagnosis is 38 years in the United States, nearly 20percent of the total cases are diagnosed after 60 years of age [10]. The diagnosis of the autoimmune disease seems to be more frequent in women (ratio 1.3-3:1). The accessibility of extremely detailed celiac serology has been critical to the interpretation of CD epidemiology. It is well known that CD is a widespread issue dependent on prevalence reports, but most reports stay underdiagnosed ('iceberg phenomenon'). The celiac disorder has a broad geographical range and impacts people of different cultural and racial origins [22]. The average prevalence of CDs in Europe has been estimated at 1%, but the prevalence ranges greatly across nations (e.g., 0.3% in Germany and 2.4% in Finland). Another of the highest prevalence rates recorded to date is 5.6% among the Saharawi people of northwest Africa. The prevalence of CD in the United States' common populations is 0.8% and has risen 4-fold in the last 40 years **[10]**. A greater number of the population live in latitudes 35 degrees north or higher of CD relative to people living in the south [23]. Celiac disease can occur at any age, even in senile populations [24]. However, new systematic observational trials have shown that most people experience celiac disease by 10 years of age **[25, 26].** The frequency of celiac disease is greater in women than in men (17.0 vs. 7.8 per 100,000 individual years in a cohort study), although this could be because men are most likely to stay underdiagnosed. A prospective study and meta-analysis observed a small rise in seropositivity among female respondents in testing trials, while some adults research indicate that men and women had equal seroprevalence. Men are less likely than women to get a duodenal biopsy during an upper endoscopy for symptoms, including diarrhoea and weight loss, leading to misdiagnosis [27]. The prevalence of celiac disease ranges across countries. In India, the incidence of celiac disease is higher in the Punjab area (1.2%) and anywhere in the north relative to the south (0.1%), despite the comparable incidence of HL Apermissive haplotypes DQ2 and DQ [28]. The celiac disorder did not differ from urban to rural regions or socio-economic background in that survey. Similarly, a study of duodenal biopsy specimens sent to pathology labs across the United States revealed that people of Punjab ethnicity had a much greater incidence of villous atrophy than people of Indian ethnicity from other parts of India [29].The factors for such ethnic and regional disparities are unclear, but they may be due to the average daily consumption of wheat, which is higher in the Punjab region [28]. It is also likely that greater than one environmental factor can responsible for regional variations. Cultural and ethnic variations still exist in celiac disease incidence, also in research trials, regardless of variations in test results. The celiac disorder was relatively less prevalent in non-Hispanic blacks and Hispanic vs. whites in the United States. Dependent on the National Health and Nutrition Examination Survey (NHANES), seroprevalence was 0.2% for non-Hispanic black and 0.3% for Hispanic persons relative to 1.0% for white individuals [30]. Similarly, considering geographical similarity, the incidence of celiac disease can differ significantly across continents. A clinical analysis finds serological signs of celiac disease in 1.4% of persons in Finland, but just 0.6% of the population in neighbouring Russian Karelia, again without major variations in acceptable HLA haplotypes. These variations have prompted researchers to evaluate environmental exposures as potential risk variables for celiac disease onset [27].

The celiac iceberg: Studies show that CD incidence is about 1% of the overall populations, with differences attributed to the higher levels of secret and atypical manifestations of the disease. Besides, the "iceberg" model can be used to show epidemiological modifications to the CD (Fig. 2). Therefore, it has been proposed that the overall scale of the "iceberg" is most or fewer the constant globally. Simultaneously, the "waterline" (the percentage of diagnosed to undiagnosed cases) will progressively change depending on the area and populations, and medical knowledge the nature of diagnostic instruments, and the degree of medical manifestations of the disorder, and so on. This affirms certain differences in the outcomes of separate demographic samples. The delivery of CDs globally cannot be accurate without Russia's information, which covers one-sixth of the world's total area. Therefore, the objective of this study is to discuss the existing evidence on CD epidemiology in Russia and provide tentative insights into this widespread chronic enteropathy [31].

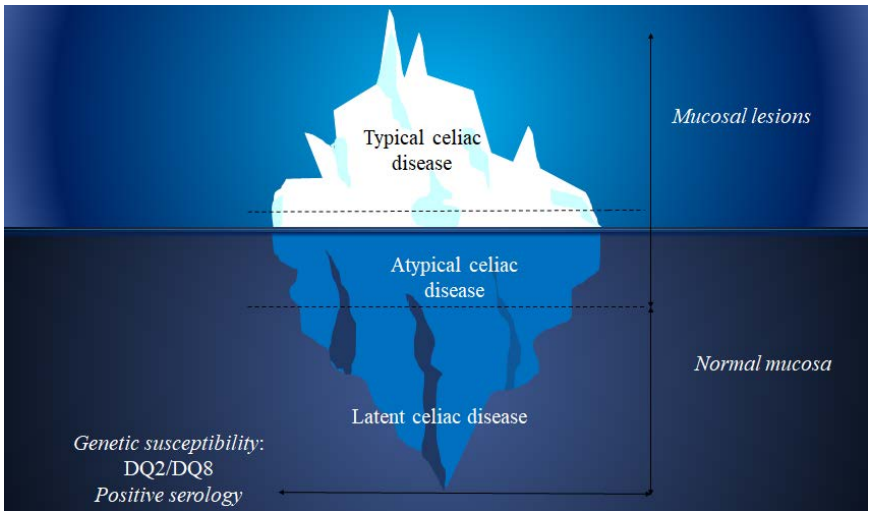

Fig 2: The celiac iceberg display epidemiological changes of CD.

Symptoms of celiac disease

Celiac disease is a chronic autoimmune condition in genetically prone individuals propagated by regular intake of gluten cereals (wheat, rye, and barley) with symptoms in the small intestine and organs outside the intestine. Patients suffering from celiac disease have gluten-induced and gluten-dependent duodenal mucosal projections (i.e., the typical crypt hyperplastic lesion with villous atrophy). Medically, these recently diagnosed individuals may or may not have gastrointestinal symptoms. Gluten-driven extra-intestinal manifestations are often the only clues to the disease. Effective serology is also the only option to classify prospective patients for upper intestinal endoscopy diagnosis. In reality, less than half of all adult patients afflicted with celiac disease report gastrointestinal symptoms at an early diagnosis. This experience comes from Finland, where adult celiac disease diagnosis has raised 20-fold in recent years, and 0.8% of the overall population has a biopsy-confirmed diagnosis. People diagnosed with celiac disease, like duodenal mucosal lesion, can have various extra-intestinal diseases [32, 33]. Dermatitis herpetiformis presents outside the intestine, is guided and based on gluten, has the same genetic history, and exists in similar families as celiac disease. In reality, one identical twin may have celiac disease, while the other is suffering from dermatitis herpetiformis. Some extra-intestinal gluten-driven celiac disease symptoms comprise osteopenia, osteoporosis, fractures **[34]**, lifelong enamel damage, arthritis, and arthralgia and also the central and peripheral nervous system, liver, and reproductive system intervention. Even autoimmune disorders can be caused by gluten, and there is a risk of malignant problems, particularly non-Hodgkin lymphoma, in undiagnosed celiac disease. The intestinal type of CD is more frequently observed in the paediatric population and children younger than three years of age. It is characterised by diarrhoea, loss of appetite, abdominal distention and failure to thrive [35]. Children and adults may complain of diarrhoea, bloating, constipation, abdominal pain, or weight loss. However, in adults, malabsorption syndrome with persistent diarrhoea, weight loss and severe asthenia is uncommon. In spite of its unusual identification; this phenotype can trigger hospitalisation due to cachexia, sarcopenia, severe hypoalbuminemia, and electrolyte irregularities. Alternatively, irritable bowel syndrome (IBS)-like constipation or alternating bowel and/or dyspepsia-like signs, such as nausea and occasionally vomiting, is more frequent [33]. By concept, celiac disease is removed in patients who have small-sized intestinal mucosal morphology at their first diagnostic endoscopy if they have a normal gluten-containing diet. It seems obvious, however, that this is not right. However, dermatitis herpetiformis is the conceptual condition managed with a gluten-free diet instead of the molecular evidence of an extra-intestinal manifestation (diseased or not). We searched the reviews to prove extra-intestinal gluten-dependent manifestations in individuals "excluded" from celiac disease [36]. Figure 3 shows the sign/symptoms of celiac disease.

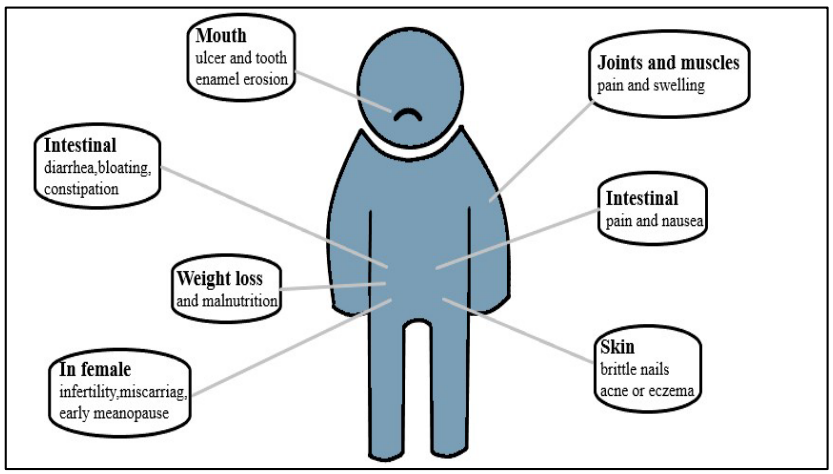

Fig 3: Symptoms of Celiac Disease

Regulatory recommendations

Celiac disease is a chronic autoimmune disorder that affects approximately 1% of the North American population [18]. People with CD usually experience a variety of physical (e.g., stomach discomfort, migraines, body aches) and/or psychological (e.g., depression, anxiety) signs. Strict adherence to a gluten-free (GF) diet is currently the only treatment for preventing short- and long-term consequences from celiac disease (e.g., infertility, intestinal cancers, osteoporosis) and is usually, but not always associated with improvements in quality of life. However, following a strict GF diet is difficult, and the evidence suggests a variation in strict adherence rates. Furthermore, many individuals with celiac disease report a reduced quality of life due to the burden of a restricted diet [37]. Many individuals with celiac disease report persistent symptoms (e.g., gastrointestinal distress) despite being on a strict GF diet [38]. The development of effective strategies to help people follow a strict GF diet, manage symptoms and cope with celiac disease is prudent. Self-regulation is regarded as a critical ability required for chronic condition patients to stick to a treatment routine Findings from recent work highlight the importance of self-regulation to assist in managing celiac disease [39, 40]. Even so, better self-effectiveness (SRE; one's belief in one's ability to self-manage their behaviors in order to consume a healthy GF diet) expects less incidents of unintended gluten intake. Research suggests that self-regulation is a skill that can be taught, which involves self-monitoring, goal-setting and planning. Current research shows that self-monitoring is an important part of modifying eating behaviors for weight loss. Furthermore, Michie and colleagues' comprehensive review revealed that the most effective interventions utilize self-monitoring in combination with one other control-theory based behaviour change technique (e.g., goal-setting, review of goals and/or progress). As a result, an evidence-based method that involves self-monitoring (i.e., of food intake and associated illness effects) and several control-theory based method (such as evaluating one's diet and symptoms through a weekly status log, a way of updating one's expectations to adopt a GF diet) may be especially useful in assisting individuals with celiac disease to adhere to a strict GF diet [41].

Probiotics, Prebiotics for Gut Microbiota Modulation in Celiac Disease Patients

Probiotics

The evidence of dysbiosis in CD patients [42, 43, 44] has gained more and more research on probiotics for gut microbiota restoration and modulation. Indeed, the composition of gut microbiota influences the spectrum of gastrointestinal symptoms of this disease [44]. Few microbiological studies [45] showed a different abundance of Lactobacillus and Bifidobacterium strains in CD patients at disease diagnosis, other than a reduction in several 'health'-promoting bacterial strains, such as Akkermansiamuciniphila, demonstrating an association with intestinal dysbiosis [46]. The unbalanced gut microbiota may indeed promote CD, influencing the mutualistic relationship between the colonic microbiota, their metabolic products, and the host immune system; to maintain immunological homeostasis, it is essential to establish a "healthy relationship" since the first years of life [47]. In support of these hypotheses, Wacklin *et al*. [48] showed that intestinal dysbiosis is linked with refractory gastrointestinal symptoms, iron deficiency, low bone density, and anemia in CD patients on GFD. The CD is strongly influenced by dysbiosis, and several theories postulate that it could facilitate a loss of gluten tolerance in genetically predisposed subjects, increasing the gut mucosal permeability, with close junction leakage and T cell recruiting throughout inflammation. Probiotics used in CD could modulate the microbiota's composition and functions; this may delay the onset of the disease or prevent it. Probiotics can also control the immune response the destruction of toxin receptors, the nutrient availability, the obstruction of adhesion sites, and the development of inhibitory substances toward pathogens [45]. According to the World Health Organization, probiotics are defined as live microorganisms, which, if administered in adequate amounts, can confer health benefits to the host [49]. Figure 1 summarizes the efficacy of probiotics in the context of CD patients. To understand the role of some bacterial clusters in the immune response's modulation, the effect of Bifidobacterium bifidum and Bifidobacterium longum on peripheral blood mononuclear cells, alone or withgram-negative bacteria, including Bacteroides fragilis and Escherichia coli, were linked to CD causes. It was found that Gram-negative bacteria induce a higher secretion of TH-1 proinflammatory cytokines and activation mechanisms (HLA-DR, CD40, IL-12, and IFN-c) for the Bifidobacterium strains **[45]**. A study conducted in Argentina found substantial changes in the amount of Lactobacillus strains in symptom-free CD infants, confirming the effects of probiotics on CD symptoms. Among the five different Lactobacilli isolated in the stools of healthy children, Lactobacillus rhamnosus, and Lactobacillus paracasei were proposed as potential probiotic strains since they show high resistance to gastrointestinal tract conditions [50]. The most widely observed bacteria in celiac disease, Lactobacilli and Bifidobacterium, can play a significant role in breaking down gluten and its harmful fragments to change their ability to trigger an immune reaction. Lactobacillus is shown to detoxify gliadin fragments after partial digestion by body enzymes, and Bifidobacteria may be able to decrease the irregular openings of close junctions according to the research summary, gluten causes junctions of the gut lining of celiac disease patients. Bifidobacterium Longum inhibits the formation of inflammatory cytokines, which are small secreted proteins produced by cells that have a particular impact on cell connections and contact. In conclusion, Bifidobacteria and Lactobacilli administration seems to have the potential to restore gut microbiota composition and predigest gluten in the intestinal lumen, reducing the inflammation associated with gluten intake, intestinal permeability, and cytokine and antibody production. These findings could explain an improvement in symptoms and quality of life in patients treated with GFD and probiotics. After all, since studies on the particular topic are already limited, international probiotic recommendations do not suggest systematic use of probiotics in medical practice [51].

Fig 4: The potential benefits of probiotics use in celiac disease patients

Prebiotics

According to the International Scientific Association for Probiotics and Prebiotics (ISAPP) consensus statement, prebiotics are defined as a substrate that is selectively utilized by host microorganisms conferring a health benefit [52]. Among the new therapies recently proposed, prebiotics are a promising and safe additive to GFD with a beneficial influence on human health. Prebiotics has the power to stimulate the growth and activity of potentially health-promoting bacteria strains in the intestine, mainly Bifidobacterium and Lactobacillus. For this motive, their capability to regulate the activity of gut microbiota could be used to address CD-related signs. Literature data lead to the hypothesis that the inclusion of prebiotics in GFD could also be easy to administer and cost-effective as an adjunctive treatment for CD [53]. Krupa-Kozak *et al*. conducted out one of first trials on the subject: a randomized placebo-controlled clinical test aimed at assessing the effect of oligofructose-enriched inulin on pediatric CD patients during GFD, called "Orafti®-Synergy1" (Tienen, Belgium) [46]. In parallel, Adebola *et al*. seen that inulin does not specifically activate any of five Lactobacillus probiotic strains. In contrast, other potential prebiotics, including lactulose and lactobionic acid, may exert this effect and represent an optimal substrate for bacteria to minimize the adverse effects of bile acid stress. Indeed, these authors found that Lactobacillus strains, in particular Lactobacillus acidophilus NCFM and Lactobacillusreuteri NCIMB 11951, have stimulating effects only in specific formulations of probiotics and prebiotics with lactulose or lactobionic acid [54]. Furthermore, another important study showed that oligofructose-enriched inulin to GFD improved the fecal microbiota, increasing the total SCFAs, such as propionate and butyrate, remarkably. This effect could be attributed to the fermentation of inulin-type fructans (ITFs) as a readily available energy source for gut microbiota present on the prebiotic formula, which is usually a mixture of short-chain fructo-oligosaccharides and long-chain inulin [46]. Among, supplementation with "Orafti®-Synergy1" may be an efficient treatment method for modifying intestinal microbiota, and it could also have potential applications in other autoimmune disorders including diabetes type I, given the presumed function of intestinal microbiota in their growth [55, 56]. Drabisnka *et al*. performed research on the efficacy of "Orafti®-Synergy1" and its impact on the metabolism and microbiota of CD children. They discovered that "Orafti®-Synergy1" improved iron homeostasis in CD patient receiving GFD, culminating in a substantial decline in plasma hepcidin concentration, which is a central regulator of duodenal iron absorption. They concluded that the addition of inulin to a GFD could be a promising strategy for the beneficial modulation of intestinal microbiota and Ca absorption improvement [56, 57, 58]. The properties of prebiotics on gut microbiota have also been clarifiedby a crossover study by Fuller *et al*. [59]. They tried to enhance the concentration of colonic Bifidobacterial populations using a commercially available prebiotic (inulin). They discovered that the fecal Bifidobacterial population was slightly greater after 16 days of therapy. In conclusion, prebiotic use in CD patients have largely not been investigated, and their use, mainly that of inulin, has been proved to enhance the abundances of 'beneficial' bacterial strains. These strains include Bifidobacterium and

Lactobacillus strains which enhance the homeostatic and metabolic activity of these strains. However, to date, sufficient data are not currently available to definitely recommend their use in routine clinical practice.

Global prevalence of celiac disease

Celiac disease (CD) is an autoimmune enteropathy caused by dietary gluten in people who are genetically predisposed to it. Until a few decades ago, the CD was considered an uncommon disease affecting mainly children and limited to European ancestry individuals. In the 1970s, the CD's diagnosis required a sequence of 3 small intestinal biopsies, but the current guidelines suggest that its diagnosis should be based on the combination of a positive celiac-specific serologic examination and small intestine biopsy specimens revealing villous anomalies. The extensive utilization serologic tests and the simplification of diagnostic requirements have enabled us to predict the true prevalence of CD in the overall populace. Over the past two decades, the CD has emerged as a major public health problem. Initial prevalence studies in the general population came from European countries, and it was estimated to affect approximately 1% of the European population. CD subsequently was reported from other parts of the world with predominant Caucasian populations such as North America, Australia, and Brazil. In the past few decades, populace centredrecords on the prevalence of CD also have been reported from the Middle East, India, and so forth. The prevalence of CD-predisposing HLA haplotypes in the general population and per-capita wheat composition, the two primary determinants of CD prevalence, vary from one region to another. However, it is unclear if there is any variation in CD prevalence in different parts of the world. Although most reviews on CD suggest that CD's global prevalence is approximately 1%, there has been no meta-analysis on this topic. A few other systematic reviews on this topic had similar limitations, and the authors of these systematic reviews did not attempt to pool the data. We conducted a systematic review and meta-analysis of the published studies on the prevalence of CD to estimate the pooled prevalence, and variation in the prevalence, of CD around the world [22]. With two of the most populous countries, India and China, in the world, the absolute numbers of patients with CD in Asia may exceed the total number of patients in Europe, and North America combined. Asia is probably the major “reservoir” of undiagnosed CD in the world. Asia has a huge landscape and population and highly heterogenous genetic, social, cultural, and nutritional practices. Similarly, there is variation in CD epidemiology, understanding, and the nature of diagnosis and care services. It is now time for Asian countries to define the extent of disease and start preparing to handle CD's impending epidemic. Alas, “Rome was not built in a single day,” and there is yet a long way to go [60].

India

In 2002, Kaur *et al*. presented the first research evaluating the history of HLA in paediatric CD patients in India. One hundred seventeen children with gastrointestinal (e.g. persistent diarrhoea, abdominal pain) and extra-gastrointestinal (short stature, iron-deficient anaemia, failure to thrive, etc.) symptoms diagnosed with CD by intestinal biopsy were analysed: most significant, almost 100% association with DQB1*02:01 in these Indian CD paediatric patients was recorded [61]. CD diagnosis has been more common in India's northern part, where the average regular consumption of wheat is the maximum [28]. Interestingly, an American survey of approximately 500,000 duodenal biopsy reports (from all over the USA) found that the ethnic group in the Punjab region (northern India) had the highest prevalence of villous atrophy among all the ethnic groups living in the world (3.08% vs. 1.80% for other Americans) [29]. At that time, this research was the first big report on paediatric CDs (including 4347 children undergoing serological testing): it showed that paediatric CDs in India were more frequent than previously considered, particularly in wheat-eating sections of India [62]. CDs are less frequently in Southern India, which have been linked to the effects of both genetic and environmental causes. Indeed, Yachha *et al*. pointed out that the incidence of HLA-DQ celiac predisposing alleles was far greater in Northern India (31.9%) than in Southern India (9–12.8%), where this genetic variation is associated with a distinct staple diet dependent on rice dishes [63].

Nutritional profile of gluten containing and gluten-free food products

Celiac disease (CD) is an autoimmune enteropathy triggered by the ingestion of gluten or related prolamins in genetically vulnerable individuals [64, 65]. CD's mean frequency in the general population is approximately 1%, but this prevalence is increasing every year worldwide. To date, the only available effective therapy is to follow a lifelong strict gluten-free diet (GFD), which will lead to progressive clinical improvement and intestinal mucosa recovery [66]. However, the adherence to a GFD may be difficult to pursue, and social life can be restricted because gluten-free products (GFP) available are more expensive and have a different taste. Social life can also be restricted because of the fear of contamination when eating outside the home. Additionally, following a GFD implies removing staples such as gluten-containing bread and pasta, which are considered mainstays in a typical Western diet. With the avoidance of these cereal-based products, a shortage of dietary fibre and several vitamins and minerals can occur unless patients do not follow a balanced diet. However, these imbalances may be difficult to assess due to rare information available in food labelling. Gluten is a mixture of proteins found in wheat, related grains and hybrids, representing the main proportion of the protein content of most of the commonly consumed cereal-based products [67]. Although gluten proteins are of low biological value, their chemical properties make them appealing for the food industry. They are the only component providing the baked products dough with viscosity and extensibility. To make it possible for CD patients to maintain a normalized diet, a series of GFP have been specifically developed and launched onto the market. Besides, GFP appeal to other population groups. GFP is made up of alternative ingredients that do not contain gluten, i.e. corn starch, potato flour/starch and tapioca flour/starch [66]. According to recent research, patients with CD have high serum cholesterol and an increasing body mass [68]. GFP are likely to be a significant part of their diets, since they are removing staple foods such as bread or pasta. Thus, some authors have suggested the nutrient composition of GFP as possible determinants of these risk factors. As of date, the only study conducted in Spain assessing the composition is from 2014 and includes 206 GFP **[64].** Today, the increase in the number of GFP available in the market and the possible incorporation of new ingredients like pseudo cereals in their manufacturing suggest an update. Millet is among the earliest

crops identified to human civilisation and may have been the first cereal grain used in the domestic activities. Millets are high in dietary fiber, phytochemicals, micronutrients, nutraceutical and are now referred to as nutricereals. Millets are flours that do not have gluten. Millets-based products can go a huge way toward alleviating gluten-related problems of gluten-sensitive people. Celiac syndrome is a gluten-sensitive endocrine disease with genetic, immunologic, and environmental causes. Gluten allergy (celiac disease) affects people around the world [69]. Thus, the need for conducting a broad study on GFP nutritional composition could be considered useful and necessary. Therefore, due to the constant update of the GFP in the market, we considered it necessary to conduct a study aimed at the stated nutrient composition analysis of the nutritional composition of available GFP and compare them with their gluten-containing counterparts (GCC) [66]. It is well recognized that adhering to a GFD allows for symptom reversal, normalization of serum antibodies, and intestinal mucosal regeneration. Thus, CD patients' nutritional status on a GFD is likely due to the nutritional quality of GF products and the food choices of CD patients. According to surveys, the nutritional condition of CD respondents after a GFD is inadequate. As a result, understanding the role of GF wheat replacements to unbalanced nutrient intakes is important. Bread and bakery products are traditionally based on flour derived from the cereal wheat, together with other temperate cultivated cereals (e.g., barley and rye), an excellent carrier of macro and micro-nutrients. In another side, certain macro and micronutrients are defective or lacking in GF flours used to make gluten free cereal products. Rice and corn, for instance, which are among the most frequently used raw materials in the formulation of GF cereal products, are poor in protein, DF and folate content [16]. Furthermore, the requirement to incorporate surface-active ingredients such as starches and/or proteinaceous and fatty ingredients such as dairy and egg proteins, as well as hydrocolloids and gums, to compensate for the lack of gluten creates dietary issues [70]. Iron, potassium, and zinc content in GF food items is lower than in GC products. Wu *et al*. have reported significantly lower protein levels in GF bread, breakfast cereals, and pasta, most probably due to the ingredients utilized (e.g., corn starch, white rice flour, potato starch or tapioca starch), which are high in carbohydrates and low in protein [71]. In the Italian market, protein levels were lower in every food category, with rusks and bread substitutes having the greatest difference [72]. From the considerations as mentioned above, it is apparent that vitamin and mineral content in GF food products should be investigated to evaluate the necessity for the fortification of GF products. The use of alternative ingredients, such as pseudocereals and legumes, should also be considered to improve GF products' protein profile. Fat, starch, sugar, and sodium elimination should be a primary concern for food technologists. Today, the increase in the number of GFP available in the market and the possible incorporation of new ingredients like pseudo cereals in their manufacturing suggest an update. Thus, the need for conducting a broad study on GFP nutritional composition could be considered useful and necessary. Therefore, due to the constant update of the GFP in the market, we considered it necessary to conduct a study aimed at the stated nutrient composition analysis of the nutritional composition of available GFP and compare them with their gluten-containing counterparts (GCC) [66].

Nutritional Deficiencies in Celiac Disease at Diagnosis and on a Gluten-Free Diet

Nutritional Status of CD Patients at Diagnosis

The nutritional profile of CD individuals at diagnosis depends on the duration of the disorder, intestinal inflammation, degree of malabsorption, and dietary consumption [73]. Malabsorption, caused by villous defects in the small intestine, resulting in various dietary deficiencies. Iron, calcium, zinc, vitamin B12, vitamin D and folate deficiencies seem to be the most common nutritional deficits reported for recently diagnosed celiac sufferers as checked by blood tests [74,75, 76, 77, 78]. Iron deficiency Anaemia is among the most common extraintestinal symptoms of CD and is seen in about 46percent of subclinical CD cases [76]. The main reason is that villous atrophy is mainly seen in the duodenum, which is also the primary source of iron absorption. Calcium deficiency and related metabolic bone disorders are also common in CD patients [77]. About 75percent of undiagnosed individual celiac sufferers have poor bone mineral density due to the absorption of calcium and vitamin D in the duodenum [76]. Calcium deficiencies can trigger growth complications and difficulty in peak bone mass production in young individuals (i.e. infants and teens). At the same time, in the elderly, it leads to a decreased mineral density and a greater chance of bone fracture [77]. The symptoms of a typical CD lead to appearance of osteopenia and osteoporosis [75]. The gastrointestinal tract is essential for homeostatic zinc regulation and requires the complex interaction of host, dietary and environmental influences. Vitamin B12 deficiency is found in 8 percent to 41percent of recently diagnosed celiac individuals, as its absorption takes place mostly in the ileum [74, 76]. The causes for the deficiency are still not clearly understood; according to some scientific researchers, they could also be associated with small intestinal bacterial overgrowth, which is also caused by small intestinal injury [73]. Deficiencies in fat-soluble vitamins A, D, E, and K have also been identified in undiagnosed CD cases [74], and osteomalacia is particularly linked to vitamin D deficiency. Shepherd and Gibson [79] correlated recently diagnosed, undiagnosed sufferers to long-term CD patients in their research, stressing excessive fat consumption (particularly saturated fat) in several men and women on CD treatment. Secondary lactose intolerance due to reduced lactase output due to the defective villi is also normal [76, 80].

Nutritional Status of CD Patients Adhering to a GFD

Replacement of gluten-containing foodstuffs with GF in the diet and subsequent improvement of CD patients' mucosal functionality may be believed to change the nutritional condition of patients on the diagnosis. Several observational research studies have examined the nutritional status of CD patients who adhere to GFD. Nutrition logs and surveys were used to determine compliance with the GFD and measure the consumption of nutrients. Nutrient consumption details were related to the prescribed dietary suggested value. Furthermore, stable participants who consumed GC foodstuffs served as guides. As far as macronutrient consumption is involved, most trials in infants, teenagers and/or adults consent to report GFD as an unbalanced diet. Fat consumption is generally higher than suggested [16]. Zuccotti *et al*. recorded lower fat consumption in CD patients than controls [81]. Shepherd and Gibson [79] discovered that after 12 months on the GFD, the average protein consumption in a female sample

group was slightly lower. Van Hees *et al*. found that celiac patients with long-term GFD eat slightly less vegetable protein than balanced controls [82]. The assessment of total plasma homocysteine has supported this low vitamin condition. Given the correlation among vitamin deficiencies elevated total plasma homocysteine rates, and cardiovascular disease, this classification may have medical consequences. However, Caruso *et al*. also observed a normalization of vitamin D and calcium levels after 1–2 years on a GFD [83]. Gluten-free products are in high demand due to the rising prevalence of celiac disease and other gluten-related disorders. Gluten reduction becomes necessary to prevent the emergence of any such condition. Gluten-free foods lack the textural, nutritional, and sensory qualities of gluten-containing counterparts. Table 1 shows some gluten free seeds used for various food preparations and their effect on food quality.

Table 1: Gluten free seeds used for various food preparations and their effect on food quality.

Seed type	Product	Quantity used	Effect on product	Reference
Oats	Cake	Oat fibre powder was incorporated into cake formulations as 5, 10, 15 and 20% replacement of rice or corn flour.	Increased β-glucan, total dietary fibre, springiness, cohesiveness, on storage decreased firmness and lightness	[84]
Chia	Cookie	10% chia seeds (CS)	Enhanced nutritional quality and on storage increases hardness of cookies	[85]
Flax	Bread	Raw and roasted ground flaxseed (5, 10, and 15 g/ 100 g) flour	Softness of bread crumb increased and causes darkness of bread crust and crumb	[86]
Fonio	Pudding	88% of fonio + 10% of finger millet and 2% of soy protein	High sensory acceptance	[87]
Brown rice	Pasta	Brown indica rice flour, 50.0 g	Improved nutrition but cooking losses and adhesiveness	[88]
Water chestnut	Pasta	10, 20, 30, 40, and 50% addition of chestnut flour	Decreased cooking time, hardness, cohesiveness, chewinese	[89]
Coconut	Flakes	Flakes with 80% cassava flour and 20% coconut waste flour are gluten-free	High dietary fiber contents	[90]
Olive	Bread	5% and 10% olive leaf	Improved quality and antifungal properties	[91]
Teff	Beer	100% raw teff	Quality attributes were acceptable and high in sweet taste	[92]
Almond	Fruit bars	Different ratios of sapodilla-wild almond seed (80:20 and 70:30 w/w) and sugar substitution with stevia (0, 1/3, and 2/3 as equivalent sweetness basis).	Higher moisture, water activity and dark in colour	[93]
Cassava	Novel non-gluten cookies	100% cassava flour	Fermentation affect aroma	[94]
Chickpea	Noodles	Noodles were prepared using rice flour with germinated Chickpea protein isolate (CPI) at ratios of 98:2, 96:4, 94:6, 92:8 and 90:10	Enhanced nutritional and cooking qualities and lightness decreased	[95]
Sorghum	Bread	sorghum flour (140 g)	Improved volume, crumb structure, texture and decreased brightness and lightness	[96]
Buckwheat	Noodles	Buckwheat flour (40, 50, 60%)	Cooking time decreased and highest swelling volume	[97]
Amaranth	Spaghettis	10% of amaranth, 50% of rice, 40% of quinoa	Texture sticky not enough firm and soft and musty taste	[98]
Pumpkin	Juice	The mixture of pumpkin and mango juices (750/ 250, v/v) received significantly ($P \leq 0.05$) high preference, followed by the blend of pumpkin, orange and strawberry juices (750/125/125, v/v/v).	Improved sensory quality of the products and promote as a functional juice.	[99]
Sesame	Cookies	Cookies with 10%, 15% and 20% banana flour (BF) and 8% sesame seeds (SS)	Improved functional characteristics	[100]
Sunflower	Muffin	Defatted sunflower seed flour (DSSF) at 15% and 30% in muffins as replacement for wheat flour.	DSSF did not affect bake loss and increased height and pore density	[101]
Hemp	Cookie	Hemp flour and corn flour at an 80:20 ratio	Improved texture and physicochemical	[102]
Quinoa	Lady finger biscuit	Quinoa flour (QF) (at 25%, 50%, 75% and 100%) with rice flour (RF)	High in proteins, lipids and improved Colour and texture	[103]

Automated diagnosis of celiac disease by video capsule endoscopy using DAISY descriptors

Celiac disease is an auto inflammatory ailment triggered in genetically susceptible individuals by consuming food containing dietary gluten. Gluten is a protein found in some grains such as wheat, barley, and rye **[104]**. In celiac disease, gluten reactivity destroys the small intestinal villi, which are primarily responsible for absorbing nutrients into the blood. Damage to the villi can result in diarrhoea, abdominal discomfort and malabsorption. The disease is present in countries globally, with a prevalence rate of about 1%. Although more celiac cases are surfacing with the advent of better diagnostic tools, a large number of cases remain undiagnosed **(**Detecting celiac disease is challenging due to its limited awareness among clinicians and patients and limited diagnostic capabilities in under-resourced countries. The

prevalence of celiac disease associated with other diseases like diabetes mellitus, thyroid and liver diseases, is high. Hence, accurate diagnosis and treatment are imperative. These reasons warrant the need for an accurate, automated diagnostic tool. Video capsule endoscopy (VCE) is non-invasive and relatively inexpensive [105]. The capsule, which is swallowed, has a video camera embedded within. This transit along the gastrointestinal tract after it is swallowed by the subject together with some water. The images obtained by the capsule during its journey along the gastrointestinal tract are recorded by a device attached to a retaining belt. The recording device is removed from the belt after about eight hours while the capsule is excreted with the faces. Once data is obtained, one can only comment on whether villous atrophy is present and if it looks severe or mild by reading the video capsule data. A quantitative classification based on the VCE image is currently not possible. Visual examination of the images from VCE is subject to inter-observer variability and has a limited spatiotemporal resolution. Hence, diagnosing celiac disease via VCE is less precise and arduous. This warrants the need for a more pragmatic, computer-aided detection (CAD) system to diagnose the disease using VCE. Herein, this study underscores the use of a computerized technique to assist in diagnosing celiac disease and summarizes the CAD systems employed in other studies. Zhou *et al*. developed unique features extracted from deep learning techniques. In our study herein, daisy descriptors are used as a cutting edge and novel method for feature extraction; before assessmenta the presence of celiac disease after concealing video image borders, feature extraction was performed via DAISY description. The features were then reduced using Shannon entropy, after which particle swarm optimisation (PSO) was executed for its proficiency in the selection of features for classification [106].

Can CD be prevented?

Many systematic reviews have shown that breastfeeding, delivery modality, and duration of gluten intake in infant diets at threat for CD may influence the disease's occurrence. Consequently, the evidence promoting these conditions in the probability of developing CDs is constrained by their prospective nature and has been criticised for alternate interpretation. Two most current seminal reports, which retrospectively tested infants with a first-degree family member with CD from childbirth, find that CD grows earlier in life in this concern population showing that earlier external conditions could be critical to the progression of CD. However, since these experiments were unable to establish specific aims for preventing CD, the gut microbiota has been identified as a key component to investigate novel prevention measures. In this section, viral (e.g., rotavirus) infections with GI can enhance the CD's concurrent production. CD's probability, especially in children with earlier (pre-6 months of age) exposure to gluten, appears substantially lower with rotavirus vaccination. To recognize possible prime reduction goals by identifying microbiome, metabolomic, and/or environmental causes that trigger a loss of gluts toleration, the on-going celiac-disease genomic, climate, microbiome, and metabolomic research has been developed to translate genetic predisposition to clinical results [107].

Future prospects

Gluten-free drugs are now a lucrative sector of the food market with an annual valuation of many billion dollars [108, 109]. The common public's erroneous belief that following a GFD is a safe lifestyle option encourages medically unwarranted gluten avoidance behaviours. Only sufferers with CD should adopt a strict GFD for the rest of their lives, and patients with IgE-mediated wheat allergy should prohibit wheat in any way. In this sense, even after several research developments, non-celiac gluten's susceptibility has been seen to be a not well-known disorder on which the scientific community has not found an agreement about its status as a separate therapeutic body [110]. While new developments have been made in the definition of alternative diagnostic biomarkers, the standard treatment guideline for non-celiac gluten sensitivity focuses on exclusion requirements for diseases such as CD or IgE-mediated wheat allergy and empirical progress after gluten reduction or GFD. Treatment can then be validated by a double-blind, placebo-controlled, cross-over gluten problem, which is the gold standard for diagnosing non-celiac gluten sensitivity [111, 112]. The key triggering compound, which mainly leads to non-celiac gluten's susceptibility, is still needed to be known since gluten can only describe a certain amount of responses and other grain ingredients, such as FODMAPs or ATIs, have been closely correlated with this disorder. Current research activities will also be needed to determine the pathogenic mechanism and disease-specific markers correlated with non-celiac gluten's susceptibility. GFD compliance without a well-defined diagnosis is baseless and can have some risks and harmful consequences as it has been shown that GFD is neither better nor advantageous than gluten-containing diets for subjects without a medically validated diagnosis of gluten-related disorders. Health doctors should also offer guidance on compliance with the GFD after an effective review of existing guidelines for diagnosing gluten-related diseases [108, 113, 114, 110].

Conclusion

Despite a significant rise in the rate of CD reports over the past 30 years, most patients remained undiagnosed. The therapy for CD is also essentially a GFD, which necessitates extensive health care, inspiration, and follow-up. Slow recovery is common, especially in people diagnosed in their adulthood. With two of the world’s most populated countries, India and China, the actual number of CD patients in Asia may outnumber those in Europe and North America combined. Asia is most likely the world's largest "reservoir" of undiagnosed CD. Early diagnosis necessitates a high level of scientific skepticism. Serologic examination firmly supports the diagnosis, and duodenal histology is advised to validate the diagnosis in most medical cases. The most successful treatment for CD is lifetime adherence to a gluten-free diet. Prolonged or recurring CD signs are not rare after beginning a gluten-free diet, and this case necessitates a thorough examination to rule out gluten contamination and other related disorders, such as RCD (refractory CD).

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