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Review

Emergence of Celiac Disease and Gluten-related Disorders in Asia

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Celiac disease (CeD) is a systemic, immune-mediated enteropathy, which is triggered by gluten protein in genetically susceptible individuals. CeD, once thought to be an uncommon disease, is now recognized to affect approximately 40-60 million people globally. While CeD is now well reported from a few Asian countries such as India, China, Pakistan, and Middle Eastern countries; it is still believed to be uncommon in the rest of Asia. Gluten-related diseases other than CeD, like non-celiac gluten sensitivity (NCGS) are also emerging globally. CeD and NCGS may present with either intestinal or extra-intestinal symptoms, and a proportion of them have overlapping symptoms with irritable bowel syndrome. Hence, many of them are misdiagnosed as having irritable bowel syndrome in clinical practice. In this review, we discuss the emergence of CeD and other gluten-related disorders, both globally and in Asia, the overlapping manifestations between gluten-related disorders and irritable bowel syndrome, and the challenges associated with diagnosis and management of CeD in Asia.
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Key Words
Epidemiology; Glutens; India; Irritable bowel syndrome; Non-celiac gluten sensitivity

Introduction

Celiac disease (CeD) is a systemic, small intestinal, immune-mediated enteropathy which is triggered and maintained by gluten protein present in cereals such as wheat, barley and rye.[1] Until a few decades ago, CeD was considered to be an uncommon disease and believed to be limited to a certain part of Europe.[2] In the absence of a good diagnostic or screening blood test, it was hard to make a diagnosis of CeD which required 3 sequential intestinal mucosal biopsies. With the advent of celiac-specific serological test for the screening and the diagnosis, the epidemiology of CeD has changed globally over the past 2 decades.[3] Furthermore, simplification of the diagnostic criteria and widespread use of celiac-specific serological tests have not only led to increase in the recognition of CeD worldwide, but also enabled us to assess the accurate prevalence of CeD in the general population.[2,4,5] Initial studies of the prevalence in the general population originated from the European countries[6,7] and subsequently regions with a predominant Caucasian population such as North America, Australia, and South American countries have also reported occurrences of CeD.[8-10] In recent times, CeD is recognized in many non-Caucasian populations including Asian and African countries.[11,12]

With 60% of the world's population, Asia is presently at the helm of understanding the epidemiology of CeD. In spite of an

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Table 1. Differentiating Features Between Celiac Disease, Non-celiac Gluten Sensitivity and Wheat Allergy

	Celiac disease	NCGS	Wheat allergy
Prevalence	0.5-2.0%	0.6-6.0%	0.4-1.0% in children
Age of presentation	Childhood and adulthood	Mostly adulthood (3rd-4th decade)	Mostly childhood (1st decade)
Sex	F > M (1.3:1-2:1)	F > M (3:1-5.4:1)	M > F
Onset of symptoms after gluten exposure	Weeks-years	Hours-days	Minutes-hours
Pathogenesis	Autoimmunity (adaptive immunity)	Poorly understood, role of both innate and adaptive immunity	Allergic immune response (IgE antibody against wheat proteins)
Clinical features			
Intestinal	Chronic diarrhea, abdominal pain, bloating	Diarrhea, abdominal pain, bloating	Less often
Extra-intestinal	Anemia Osteoporosis Neurological symptoms (ataxia, peripheral neuropathy) Growth retardation	Tiredness Lack of well-being, headache, foggy mind, fatigue Numbness of limbs Joint/muscle pain Fainting Oral/tongue lesions	More often Skin rashes urticaria Angioedema, asthma, cough
Serology	IgA anti-tTG Ab IgA anti-EMA IgA anti-DGP Ab	IgG Anti-gliadin Ab	IgE antibody to wheat protein
Gastroduodenoscopy	Scalloping, grooving of duodenal folds	Normal	Normal
Histology	Various grades of villous atrophy with crypt hyperplasia	Normal/increased intra-epithelial lymphocytes	Normal
Treatment	Gluten-free diet	Gluten free diet	Wheat restriction
Spontaneous resolution	No	Not known	65% by 12 years of age

NCGS, non-celiac gluten sensitivity; F, female; M, male; Ab, antibody; tTG, tissue transglutaminase; EMA, endomysial antibody; DGP, deamidated gliadin peptide; FODMAP, fermentable oligosaccharides, disaccharides, monosaccharides, and polyols.

increase in the publications on CeD from Asia, there is a dearth of data on population-based prevalence from most nations, except for India and China.[10,13-19]

It is not only CeD which has caught the eye of clinicians and clinical scientists, the spectrum of wheat and or gluten-related disorders has also expanded in recent times. The widespread consumption of wheat makes the disorders related to gluten relevant for most of the world including Asia. The broad spectrum of gluten-related disorders includes:

- Autoimmune diseases: CeD, dermatitis herpertiformis, and gluten ataxia
- Non-autoimmune, non-allergic disorder: non-celiac gluten sensitivity (NCGS)
- IgE mediated allergic reactions: classic wheat allergy, wheat-dependent exercise induced anaphylaxis, and occupational asthma (baker's asthma)

These gluten-related disorders differ in their pathophysiology and their clinical symptomatology, which are summarized in Table 1.[20-26]

The phenotypic spectrum of CeD is diverse including classical and non-classical CeD. Those with typical signs and/or symptoms of malabsorption such as diarrhea, weight loss, vitamin deficiencies, or malnutrition are classified as classical CeD. Patients with non-classic CeD are difficult to recognize as they present with non-gastrointestinal symptoms such as short stature, anemia, amenorrhea, or osteopenia/osteoporosis. A significant fraction of patients is asymptomatic or have non-specific mild complaints which are managed symptomatically for prolonged duration. These patients with CeD having mild gastrointestinal symptoms may fulfill the criteria for the diagnosis of functional gastrointestinal diseases, mostly irritable bowel syndrome (IBS). This may lead to a missed diagnosis and may be treated as IBS.

Methods

We searched the PubMed using the terms "celiac disease," "gluten sensitivity," or "non-celiac gluten sensitivity," "irritable bowel syndrome" or "functional gastrointestinal disease," "epidemiology," "prevalence," "risk factors," "clinical manifestations," or "overlap." Abstracts were screened and articles which had relevant information on celiac disease or its associated disorders in any of the Asian countries were included. The search was extended by using the references of selected recent articles and systematic reviews or meta-analysis.

Changing Epidemiology of Celiac Disease

Global Prevalence of Celiac Disease

The prevalence of CeD in a population can be assessed using 2 methods. One way is to assess the seroprevalence of CeD, which is done using celiac-specific serological tests, and the proportion of people having a positive test is defined as seroprevalence in a population or a community. The prevalence of confirmed CeD is assessed using a combination of serological tests specific to CeD and demonstration of villous abnormalities using duodenal mucosal biopsies. We, in a recent systematic review and meta-analysis of population-based studies, including 275 818 subjects, have shown a pooled global seroprevalence of CeD to be 1.4% (95% CI, 1.1-1.7%).[14] The global pooled prevalence of biopsy-confirmed CeD was found to be 0.7% (95% CI, 0.5-0.9%), meaning thereby 1 in 140 individuals have CeD. The differences in the seroprevalence and prevalence of biopsy-confirmed CeD is mainly because lack of confirmation of presence of villous abnormalities in seropositive individuals by endoscopic mucosal biopsies in many studies.[27,28]

The prevalence of CeD varies from continent to continent, the highest being in Europe. On stratification of countries into quartiles based on the prevalence of biopsy-confirmed CeD, countries with highest prevalence (76th to 100th quartile) include Argentina, Egypt, Hungary, Finland, India, New Zealand, and Sweden, and countries with lowest prevalence (0 to 25th quartile) include Brazil, Germany, Republic of San Marino, Russia, and Tunisia.[29]

Based on above mentioned prevalence data, approximately 40-60 million individuals have CeD globally and of those, the majority (83-95%) are in developed countries, and even larger numbers in the developing countries still remain undiagnosed.[30]

Celiac Disease in Asia

The epidemiology of CeD is different in different parts of Asia due to the heterogeneity of population, genetics, economic condition, and dietary habits (Figure).[31-36] A recent systematic review and meta-analysis showed that the pooled prevalence based on serological tests (IgA anti-tissue transglutaminase (tTG) antibody [Ab] and/or anti-endomysial antibodies [EMA]) of CeD in Asian countries was 1.6% among 47 873 participants. The pooled prevalence of biopsy proven CeD was 0.5% in 43 955 individuals.[37]

In a multicenter pan-India study including 23 331 healthy adults the age adjusted seroprevalence of CeD was 1.23% in Northern India, 0.87% in North-eastern India, and 0.10% in Southern India. This study demonstrated regional differences in the prevalence of CeD which was likely because of difference in the wheat (gluten) eating pattern, being highest in the Northern part of India and lowest in the South. Genetic differences like population prevalence of predisposing gene for CeD such as human leukocyte antigen (HLA)-DQ2 and/or HLA-DQ8 are unlikely to explain such a significant difference.[11]

The interest in CeD in China was sparked by a systematic review and meta-analysis of the predisposing genes for CeD done by Yuan et al[33] who had predicted that CeD should not be uncommon in China. Two studies on the prevalence of CeD have been published from China after the publication of the above mentioned systematic review. In a recent cross-sectional study, 19 778 Chinese youth (age 16-25 years) from 27 regions were recruited at 2 universities in Jiangxi, China, from September 2010 through October 2013. They were all tested for IgG against deamidated gliadin peptides (IgG anti-deamidated gliadin peptide), and IgA anti-tTG Ab. The prevalence was dramatically higher (12-fold) in the Northern provinces, where wheat was the staple diet. The seroprevalence of CeD in the Shandong province was 0.76% (95% CI, 0.21-1.95%), similar to the rest of the world.[29] In another recent study including 2277 in-patients with gastrointestinal symptoms in 4 major ethnic groups of Xinjiang Uyghur Autonomous Region, China (1391 Han, 608 Uyghur, 146 Kazakh, and 132 Hui), the seroprevalence and prevalence of biopsy-confirmed CeD was found to be 1.27% (95% CI, 0.81-1.73%) and 0.35% (95% Cl, 0.11-0.59%), respectively.[38] The frequency of the HLA-DQ2 and/or DQ8 haplotype ranged from 40.0-52.1% in that region. The rural parts of China, where wheat consumption was higher than the urban part, had 3 times higher prevalence of CeD (3.16% vs 0.97%, $P < 0.01$). Interestingly, of 246 patients with diarrhea-predominant IBS in China, 2.85% were diagnosed to have CeD.[39] These preliminary

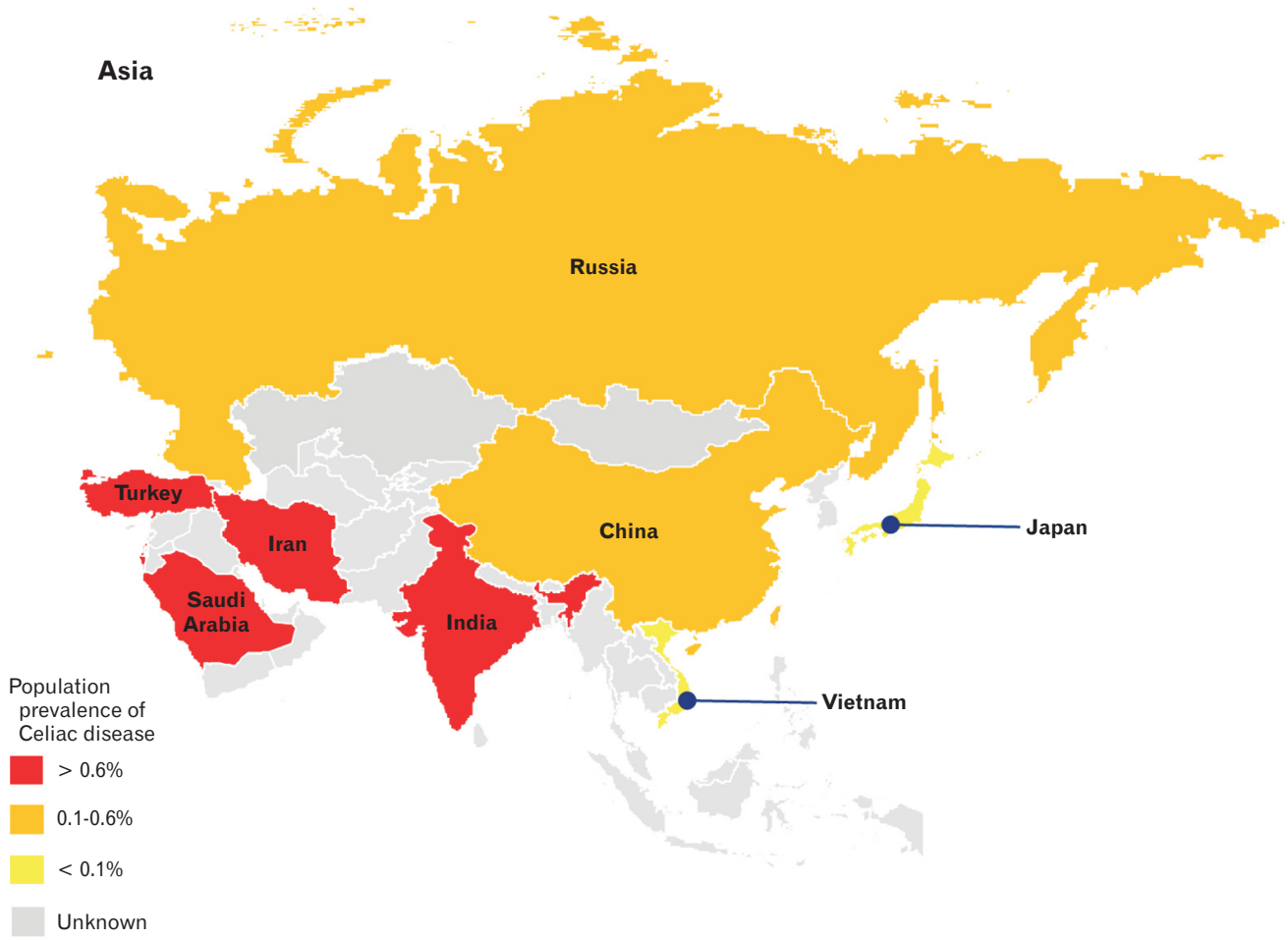

Figure. Map of Asia showing population prevalence of Celiac disease across Asia.

studies establish the foundation for exploration of the exact prevalence of CeD and the regional geographical differences in China.

In a relatively small study including 562 young healthy volunteers from Malaysia, a seroprevalence of CeD was found to be 1.25% (95% CI, 0.78-1.72%). In this multi-ethnic country, all 3 ethnic group such as Malay (0.8%), Chinese (1.7%), and Indian (1.3%) were affected.[40]

In a study from Japan, 12.8% and 13.4% of 172 patients with inflammatory bowel disease were found to have anti-tTG Ab and anti-deamidated gliadin peptide Ab respectively, in comparison to 1.6% and 0.5% in the same number of controls.[34] Although this did not correlate well with biopsies as many patients had an increase in intraepithelial lymphocytes, none had villous atrophy. A subset of the inflammatory bowel disease patients who were put on gluten-restricted diet showed a reduction in the antibody titres, as well as improved activity scores of inflammatory bowel disease. In another study including 2008 subjects, anti-tTG Ab was found to be in a high proportion (8.0%), none of them however were EMA positive and only 1 demonstrated changes suggestive of CeD on duodenal biopsy.[41] Another study including 1961 Vietnamese children showed that 1.0% of them had anti-tTG ab, but none of them were EMA positive.[42]

Few counties in Asia have not formally reported CeD, including Indonesia, Korea, and Taiwan.[43,44]

Increase in the Incidence of Celiac Disease

Not only the prevalence, but incidence of CeD has also increased throughout the Western world. The pooled average annual incidence of CeD has been rising by 7.5% (95% CI, 5.8-9.3) per year over the past several decades. A recent systematic review reported the pooled incidence of CeD in women and men to be 17.4 (95% CI, 13.7-21.1) and 7.8 (95% CI, 6.3-9.2) per 100 000

person-years, respectively.[45]

The increase in the incidence in CeD is due to improved diagnostics and higher awareness about the disease amongst physicians and changes in our environment. Improved hygiene and a decrease in the exposure to microbes early in life has been postulated to induce an overactive immune response later in life, and thus many autoimmune disorders, including CeD.[46]

Risk Factors That Might Determine Prevalence of Celiac Disease in Any Population

The pathogenesis of CeD involves a complex interplay of environmental and genetic factors. Based on the prevalence of the high risk categories in these factors, hotspots of the world for CeD can be identified.[47]

The 2 most populous countries of the world, India and China, also grow the maximum amount of wheat grains. Indian's consume an average of 48.0 kg/person/year.[48] In contradiction to usual belief, the per capita consumption of wheat flour in rural Chinese households is 59.6 kg and much higher than that in urban Chinese households (12.5 kg).[33] Furthermore, increasing Western influence in the diet and use of commercial gluten-based foods like breads, noodles, and pasta is leading to increase consumption of gluten intake in many Asian countries. The ingestion of gluten is further accentuated by urbanization of small towns, migration to busy metropolitan cities, and culture of fast food restaurant dining. An increase in gluten ingestion is likely to increase chances of development of CeD in genetically susceptible populations.[33]

Over the years, it has become clear that CeD is not a monogenic disorder. The HLA alleles which have been shown to pose the highest risk for CeD and are found in more than 95% of CeD are HLA-DQ2 (*HLA-DQA1*0501* and *HLA-DQB1*0201*) and HLA-DQ8 (*HLA-DQA1*0301* and *HLA-DQB1*0302*).[49-54] The biological plausibility of this predisposition is explained by the high affinity of deamidated gliadin peptides to HLA-DQ2 and HLA-DQ8 molecules.[53] The contribution of these 2 genes is alone enough to account for 40% of the heritable risk of developing

Table 2. Spectrum of Clinical Manifestations and Associated Autoimmune Diseases in Celiac Disease

	System	Manifestation
Classical manifestations	Intestinal	Chronic diarrhea
		Bloating
		Generalized fatigue
Non-classical manifestations	Cutaneous	Dermatitis herpetiformis
		Vitiligo
	Endocrinological	Short stature
		Infertility
		Delayed menarche
		Amenorrheal
	Hematological	Anemia
		Thrombocytosis
	Hepatic	Hypertransaminesemia
		Autoimmune hepatitis
		Cirrhosis of liver
	Muscular	Tetany
		Weakness
	Neurologic	Cerebellar ataxia
		Peripheral neuropathy
		Seizures
	Skeletal	Osteopenia, osteomalacia, and osteoporosis
		Pathologic fractures
	Dental	Dental enamel defects
	Psychiatric	Autism spectrum disorder
		Anxiety disorder
		Attention deficit hyperactive disorder
		Mood disorder
		Schizophrenia

CeD.[54,55] Homozygosity of HLA-DQ2 depicts a gene-dose effect and is a predictor of complicated CeD like refractory disease or malignant transformation.[54,55] It must be noted though, that approximately 40% of the Western population also carry these haplotypes without ever developing CeD, and thus HLA-DQ2 and DQ8 are necessary but not sufficient for CeD to develop.[1]

In a meta-analysis of HLA-DQ2 and -DQ8 haplotype in China, it was reported that HLA-DQ2 was more prevalent in the Northwestern than in the Southeastern populations of India which correlates with the reported prevalence of CeD in these regions.[33] In other Asian countries such as Japan, Taiwan, Korea, and Indonesia the frequency of predisposing HLA allele is low (< 5%).[56]

Manifestations of Celiac Disease

CeD has a myriad of clinical manifestations and the spectrum includes asymptomatic potential CeD, classical CeD, and non-classical CeD. The clinical features of classical and non-classical CeD are presented in Table 2.[57]

Non-celiac Gluten Sensitivity

NCGS is an evolving entity defined by intestinal and/or extra-intestinal symptoms related to wheat ingestion in individuals in whom CeD and wheat allergy has been excluded.[57,58] NCGS is also termed as "gluten sensitivity," "gluten hypersensitivity," or "non-celiac wheat sensitivity." There is a wide spectrum of manifestations of NCGS, both extraintestinal and intestinal (Table 1). Epidemiological data on NCGS is still sketchy but experts believe that it is more common than CeD.[59] The prevalence of NCGS ranges from 0.6-10.6% and this wide range of prevalence is mainly because of varying definitions of NCGS used in studies.[59] Lack of data on the true prevalence of NCGS is primarily due to 2 reasons. Firstly, there is no specific biomarker for NCGS, and making of a diagnosis of NCGS requires a rigorous protocol including an initial gluten-free diet followed by double blind placebo-controlled food-challenge with cross over.[58] Secondly, many people avoid gluten for symptom relief without medical advice or consultation and rely on self diagnosis. At present, there is a dearth of data on the prevalence of NCGS in Asian populations.

Overlap Between Gluten-related Disorders and Irritable Bowel Syndrome

The clinical demarcation between IBS, CeD and NCGS is not very clear. A recent meta-analysis including 22 studies with 6991 patients with IBS has shown that 3.3% (95% CI, 2.3-4.5%) of them had CeD.[60] Interestingly the pooled prevalence of CeD also varied significantly with IBS subtype. As expected, the prevalence of CeD was the highest in patients with IBS-D (pooled prevalence of 5.4%; 95% CI, 3.3-7.8%) and mixed IBS 3.1% (95% CI, 1.7-5.1%), and lowest in those with constipation-predominant IBS 1.8% (95% CI, 0.9-3.0%). A couple of points merit mention here. Firstly, most of the studies, except for one, originated from secondary or tertiary-care referral centers, hence the data may not be applicable to IBS population as a whole. Secondly, 20 of 22 studies originated from Europe and Asia with pooled prevalence of 3.9% (95% CI, 2.1-6.3%) and 3.7% (95% CI, 2.2-5.6%), respectively. Studies from North America have not found an increased seroprevalence of CeD among patients with IBS. Thus, the prevalence of CeD in patients with IBS may vary with geographic regions.

Since the prevalence of CeD in patents with IBS is higher than the general population, especially diarrhea-predominant IBS (IBS-D) and mixed IBS, these patients should be screened for CeD.[61] Not only CeD, some of the patients with IBS may have NCGS, however there is no screening test for NCGS at the present point of time. While the diagnosis of CeD is based on a combination of a positive celiac specific serological test and demonstration of villous atrophy on intestinal mucosal biopsies, diagnosis of NCGS however requires symptom response on gluten withdrawal and reappearance of symptoms on rechallange with gluten in a double blind fashion. Furthermore, it is well known that certain foods including wheat are the triggers of symptoms in patients with IBS.[62] Symptomatic improvement has been seen in a significant proportion of patients with IBS-D with the exclusion from gluten from their diet. This is supported by the reduced stool frequency with gluten-free diet in IBS-D patients (n = 45) in a randomized trial.[63]

Wheat is composed of both gluten and fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAP).[64] Both randomized- controlled trials and meta-analysis of randomized controlled trials have demonstrated symptomatic improvement in a third of IBS patients with low FODMAP diet.[65] Since ingestion of wheat is also restricted in patients prescribed a low FODMAP diet, a low FODMAP diet leads to reduction in gluten intake because they tend to co-exist in wheat. Similarly, a diet devoid of gluten also leads to low FODMAP ingestion.[66]

It is still debatable as to which component of wheat causes symptoms in patients having IBS-like symptoms and NCGS. The leading candidates which are suspected are gluten and fructans. This has been explored by 2 randomized controlled trials.[64,67] In

the first double-blind cross-over trial including 37 patients with NCGS and IBS, patients were randomly assigned to high-gluten (16 g gluten/day), low-gluten (2 g gluten/day plus 14 g of whey), or control (16 g whey protein/day) for 1 week, following 2 weeks of low FODMAP diet. After a washout period of at least 2 weeks they were crossed over to other diet.[67] In all the study subjects, gastrointestinal symptoms improved consistently and significantly during low FODMAP diet, but significantly worsened to a similar degree when they were put again on gluten or whey protein, suggesting a contribution of anticipatory "nocebo" response to gluten challenge in these individuals with perceived gluten sensitivity. In another randomized, double-blind cross-over challenge trial, 59 patients with NCGS were provided gluten, fructans, or placebo, concealed in museli bars. The patients randomized to fructans showed significantly higher overall gastrointestinal severity score than those randomized to gluten or placebo.[64] Since wheat contains both gluten and FODMAP, patients reporting symptoms on wheat restriction may have obtained benefit in their symptoms because of lower intake of FODMAP (fructans) rather than gluten restriction. Another possibly implicated component of wheat in causation of is amylase trypsin inhibitors, which have a potential of activating the innate immune system via toll-like receptor 4 pathways. However, its clear role in IBS has yet to be determined.[68] In addition to components of wheat, intestinal dysmotility has also been implicated in the pathogenesis of both IBS and NCGS.[69]

While a small proportion of patients with IBS may have CeD, as discussed above, almost one third of patients with CeD who are on gluten-free diet do complain of some GI symptoms, which mimics IBS-type symptoms.[61]

Discussion

While CeD is emerging in many Asian countries, there is very limited preparedness to handle these patients in Asia. A welcome step was made when a working group of 13 members from the Asia-Pacific region and World Gastroenterology Organization reviewed relevant literature on issues specific to the Asia-Pacific region for the diagnosis and management of CeD and recommended possible solutions.[70] Furthermore, the Asia-Pacific Association for Gastroenterology has created a formal working group on celiac disease to conduct relevant research to unravel the burden of CeD in Asia. We have recently reviewed the challenges in the awareness about CeD in Asia, the availability of the diagnostic tests, and management-related challenges such as availability of trained dieticians and availability of reliable gluten-free products in Asia.[70]

One of the most important priorities about CeD is Asia is to explore and estimate the prevalence of CeD in many Asian countries and increase in the awareness about this disease amongst gastroenterologists, internists, pediatricians, pathologists, and primary care physicians.

Celiac-specific serological tests are the center stage of both the screening of the suspected patient and in the diagnosis of CeD. Currently, most of the celiac-specific serological test kits are imported from Europe and North America. These tests have their diagnostic accuracy evaluated for Caucasian populations and thus, the cut-offs of the antibody levels are determined for these populations. With a difference in the genetic make-up and the amount of gluten ingestion, the cut-offs for a positive test determined for the Caucasian population may not apply to Asian populations. In another study, we have observed different cutoff values of the IgA anti-tTG Ab test between North American and Indian patients with CeD.[71]

The successful management of CeD is primarily dependent on a combination of factors involving the understanding of disease by the patient as well as following the prescribed dietary restrictions. There is a dearth of trained dietitians in Asia to adequately counsel these patients. Due to this dearth, it is important for physicians to know more about the practical aspects of prescribing a gluten-free diet. This includes not just restriction of foods but also advising a well-balanced diet tailored to each individual patient.[72,73] There is also a need for availability of reliable gluten-free food in the food supply chain and legislation for maintenance of quality control of gluten-free food in the Asian food industry.

Conclusion

In conclusion, the total number of patients with CeD in Asia, because of large its population, is likely to overtake the total numbers of patients in rest of the world. There is a need to recognize presence of CeD in Asian countries, and such Asian countries should start preparing to handle the emerging epidemic of CeD in Asia.

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