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WORKING PARTY REPORT

Issues associated with the emergence of coeliac disease in the Asia–Pacific region: A working party report of the World Gastroenterology Organization and the Asian Pacific Association of Gastroenterology

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Abstract

Background and Aim: Once thought to be uncommon in Asia, coeliac disease (CD) is now being increasingly recognized in Asia–Pacific region. In many Asian nations, CD is still considered to be either nonexistent or very rare. In recognition of such heterogeneity of knowledge and awareness, the World Gastroenterology Organization and the Asian Pacific Association of Gastroenterology commissioned a working party to address the key issues in emergence of CD in Asia.

Methods: A working group consisting of members from Asia–Pacific region, Europe, North America, and South America reviewed relevant existing literature with focus on those issues specific to Asia–Pacific region both in terms of what exists and what needs to be done.

Results: The working group identified the gaps in epidemiology, diagnosis, and management of CD in Asian–Pacific region and recommended the following: to establish prevalence of CD across region, increase in awareness about CD among physicians and patients, and recognition of atypical manifestations of CD. The challenges such as variability in performance of serological tests, lack of population-specific cut-offs values for a positive test, need for expert dietitians for proper counseling and supervision of patients, need for gluten-free infrastructure in food supply and creation of patient advocacy organizations were also emphasized.

Conclusions: Although absolute number of patients with CD at present is not very large, this number is expected to increase over the next few years or decades. It is thus appropriate that medical community across the Asia–Pacific region define extent of problem and get prepared to handle impending epidemic of CD.

Introduction

Advances in medicine are made when astute individuals make observations that have previously eluded others, or when techniques are developed to investigate hypotheses that previously could not be explored. In 1888, the English physician and pediatrician Samuel Gee put coeliac disease (CD) on the map with his paper *On the coeliac affection*.[1] In this account, he accurately described the clinical features in children with CD and predicted with prophetic insight that cure would come from manipulation of the diet.

There has been significant advancement in the knowledge related with CD in the past two decades.[2,3] Once thought to be rare and only to occur in Western Europe, CD is now considered a relatively common disease affecting about 0.6–1% of the world's population.[2–5] After Europe, America (both North and South) and the Middle East, it is now being increasingly recognized in the East, including many Asian countries.[2,4–10] Also, once thought to be a disease affecting children exclusively and, therefore, to be managed mainly by pediatricians, CD is now known to affect all age groups including the elderly; more than 70% of new patients are diagnosed above the age of 20 years old.[11,12] Despite its worldwide prevalence, the level of awareness of this condition is unfortunately low among health-care professionals, including general physicians, family physicians, internists, gastroenterologist, and pathologists. Thus, many cases are either missed or detected rather late.

The Asia–Pacific region is currently at the crossroads of the frontier of knowledge and awareness of CD. Although there has been an increase in the number of publications on CD from the Asia–Pacific region, there is a paucity of literature on its prevalence in most Asian nations, with the exception of Australia, New Zealand, Iran, and India.[13–18] Additionally, few case reports and short reports are available from China, Pakistan, and Japan.[19–26] In many Asian nations, CD is still considered to be either nonexistent or very rare. In recognition of such heterogeneity of knowledge and awareness, the World Gastroenterology Organization (WGO) and Asian Pacific Association of Gastroenterology (APAGE) commissioned a working party to address the key issues in the emergence of CD in Asia.

Methods

A working group of 13 members from the Asia–Pacific region, Europe, North America and South America was formed. Twelve members participated in a face-to-face meeting in New Delhi in April 2013. Topics were assigned to individual members who reviewed the relevant existing literature with focus on those issues specific to the Asia–Pacific region both in terms of what exists and what needs to be done. After each presentation, an in-depth discussion occurred and salient points were gathered and recorded. A draft manuscript based on the reviews and discussions was circulated among the working group members for their comments and approval. The final report was structured to summarize current concepts in CD and then to define specific issues of relevance to the Asia–Pacific region.

Epidemiology

The epidemiology of CD continues to evolve with improved diagnostic measures. In Europe and North America, the mean frequency of CD in the general population is around 1%.[2,3,5,6,27] However, there is large intercountry variability; for example, the prevalence of CD is as high as 2–3% in Finland and Sweden, while it is only 0.2% in Germany.[28] Despite sharing a similar distribution of causal factors (level of gluten intake and frequency of human leukocyte antigen (HLA) CD-predisposing genotypes HLA-DQ2 and -DQ8), reasons for such heterogeneity are unknown.

The knowledge of the epidemiology of CD across Asia–Pacific is limited.[9,10,15–17] In Australia and New Zealand, disease prevalence mimics that of Europe. In India, CD was recently described by an Indian task force as being "submerged in an ocean of malnutrition."[29] Its frequency in India seems to be higher in the Northern part of the country, the so-called "coeliac belt", a finding that is at least partially explained by the wheat-rice shift from the North to the South.[30,31] A recent study in the Delhi area applied a three-step clinical/serological screening procedure. With a large population sample ($n = 2879$), the prevalence of CD prevalence was 1.04% (1 in 96) and of a positive anti-transglutaminase antibodies (anti-tTG) to be 1.44% (1 in 69).[10] In a questionnaire-based survey of 4347 schoolchildren (3–17 years) from Ludhiana, a city in Northern part of India, the prevalence was 1 in 310.[9] Serological positivity was 1:179 (0.56%) among apparently healthy blood donors ($n = 1610$).[32] Based on these data, it is estimated that 5–8 million people can be expected to have CD in India, yet only a few thousand cases appear to have been diagnosed so far.[9,10,33,34] There is clearly a need for further epidemiological studies to determine regional differences in prevalence of CD in India.

With more than 1.3 billion people, China is the most populous nation and the second largest by land area in the world. Both the major causative factor—gluten consumption (particularly in the Northern part of the country)—and at-risk HLA genotypes—HLA-DQ2 and -DQ8 (albeit with a lower prevalence than in Western countries)—are found across China.[29,35] Nevertheless, evidence for the existence of CD is limited to five reports of a small number of cases.[19,20,23–25] For example, in a recent series of 118 children with chronic diarrhea admitted in pediatric hospitals in four major Chinese cities (Shanghai, Wuhan, Jinan, and Chengdu), serology and duodenal biopsy results were consistent with CD diagnosis in 14 patients (11.9%).[20] These reports are of great importance in that they confirm the occurrence of CD in China, a country where CD was previously thought to be nonexistent. In Japan, coeliac-specific antibodies (anti-tTG or anti-deamidated gluten peptide) were present in 18% (31/172) of patients with inflammatory bowel disease compared with the healthy control population of 1.6% (3/190).[26] However, none had biopsy- or HLA-defined CD in either group. Finally, there are no formal reports on CD from Malaysia, Indonesia, Korea, Taiwan, Philippines, and any of the smaller Pacific islands, where incidences may be less because of low wheat consumption, a low frequency of HLA-DQ2, and very limited availability of celiac specific serological testing.

The presentation of CD

Gluten hypersensitivity in CD was initially thought to be limited to the intestine and all other features were considered to arise secondary to malabsorption. However, CD is now considered a multisystem disorder with systemic inflammation potentially affecting many organs of the body such as skin, brain, liver, and bones.[36–39] Such effects may present with minimal intestinal involvement. What was regarded as the classical presentation of gut symptoms with evidence of malabsorption now represents at most 50% of patients.[14,40] This has important implications for recognizing the condition.

Classical CD. CD can present to a clinician at any age starting from early childhood to the older adults. Infants and young children typically present with chronic diarrhea, abdominal distension,

failure to thrive, poor appetite, and irritability between 6 to 24 months of age after the introduction of gluten in their diet.[3,13,41] In adults, the classic gastrointestinal manifestations include diarrhea, steatorrhea, excessive flatulence and abdominal distension, weight loss, malaise, and recurrent aphthous ulcers.[40,42,43] However, gastrointestinal symptoms can also mimic those of irritable bowel syndrome with constipation and bloating predominating.[44–46]

Atypical CD. The atypical form is characterized by minimal or absent gastrointestinal symptoms and signs with characteristic villous atrophy.[3] This form of the disease is more often recognized in older children and adults, and may represent just the "tip of an iceberg."[31] As it seems now to be more common than the classical form, the term, "atypical," may now not be appropriate. Its manifestations vary and have been reviewed elsewhere.[47] The more common manifestations are as follows:

- *Hematological manifestations:* Anemia is common and several studies from Europe, North America, and India have suggested that iron deficiency with or without anemia may be the sole manifestation of CD.[3,40,43,48–50] While iron deficiency is the commonest cause of anemia, untreated subjects with CD can have folic acid and, less commonly, vitamin B12 deficiency.[50,51]
- *Endocrinological manifestations:* Although CD is a known cause of short stature/failure to thrive, it has been poorly recognized in many countries including India. The prevalence of CD in short statured children ranges from 2–8% around the world.[52] In a recent study from the Northern part of India that included 176 patients with short stature, 27 (15.3%) of short statured cases were due to CD.[53] Furthermore, the same authors reported a significant increase in CD as an etiology of short stature from about 1.6% to 13.7% over the past decade.[54] This increase might be attributed to an increased awareness about CD and the availability of serological tests for screening for CD. Because a timely diagnosis of treatable causes can lead to an increase in growth velocity and the potential for attaining near normal height, increased awareness of and investigation for CD in children and adolescents is needed.[55]
- *Involvement of the liver:* The liver is reported to be affected in 15–61% of patients with CD, usually manifesting as an asymptomatic increase in serum transaminases, which normalizes in most of the patients (80%) on gluten free diet (GFD).[43,56,57] Non-cirrhotic portal fibrosis, autoimmune hepatitis, primary biliary cirrhosis, primary sclerosing cholangitis and even cryptogenic cirrhosis are also known to occur in patients with CD.[56,58–61] The prevalence of CD among patients with autoimmune hepatitis ranges from 2% to 20%.[56,58] In a Swedish study of 327 patients with chronic liver disease, the prevalence of CD was 15 times higher compared with the general population.[60] Among 185 patients who underwent liver transplantation, eight patients had CD.[61] Furthermore, three of four adult patients with severe hepatic dysfunction who were diagnosed with CD while waiting for liver transplantation were removed from the liver transplantation list upon marked improvement of hepatic dysfunction after being placed on GFD.[61] This underlies the importance of diagnosing CD in patients with hepatic dysfunction.
- *Osteoporosis and osteomalacia:* CD predisposes a patient to low bone mineral density (BMD) at all sites of the skeleton and 26–72% of patients with CD have osteoporosis or osteopenia.[62,63] Conversely, 4.5–12% of patients with low BMD and idiopathic osteoporosis have CD.[64,65] Furthermore, some patients with osteomalacia are reported to have CD.[66]
- *Neurological manifestations:* CD has been associated with neurologic and psychiatric disorders, including cerebellar ataxia, peripheral neuropathy, epilepsy, dementia, and depression, in 6–10% of patients.[67,68] Neurological manifestations occur because of two main reasons. First, they may be secondary to the malabsorption caused by CD. Secondly, some neurologic syndromes may reflect extraintestinal manifestation inflammatory responses to gluten sensitivity with or without intestinal involvement.[67,68] Gluten ataxia is one of the most common of these and is defined as an apparently sporadic ataxia with positive serological markers for gluten sensitivity [anti-gliadin antibodies (AGA), antibody against tissue transglutaminase-6].[68]

Investigation of CD

Who should be investigated? There are three situations where patients should undergo investigations for CD.

- *Patients with clinical manifestations suggestive of CD:* These might include patients with chronic or intermittent diarrhea, failure to thrive, weight loss, stunted growth, delayed puberty, amenorrhea, iron-deficiency anemia, persistent fatigue, dermatitis herpetiformis-like rash, fracture with inadequate traumas/osteopenia/osteoporosis, infertility, ataxia, or an unexplained increase in transaminase.[2,69–72]
- *Patients with conditions that are associated with a higher risk of CD, but where CD might not be pathogenically related to that condition:* These might include type 1 diabetes mellitus, autoimmune thyroid disease, autoimmune liver disease, Down's syndrome, Turner's syndrome, Williams' syndrome, and selective immunoglobulin A (IgA) deficiency.[2,69–72]
- *First-degree relatives of patients with CD:* Because first-degree relatives are at 4- to 12-fold higher risk for CD, all should be screened for CD.[2,69–75]

Diagnostic tests in CD

Coeliac-specific serological tests. Coeliac-specific serological tests are the cornerstone for screening of patients for CD, while most current definitions of CD are based on the histological demonstration of enteropathy.[76,77] Serology is, therefore, generally regarded as a "surrogate marker" for the diagnosis of CD. It should be emphasized that all serological tests are dependent on continuous dietary intake of gluten, as they all tend to normalize over months after commencement of a GFD.[78] Furthermore, transient positive serology has also been observed both in adults and children.[79–81]

There are several coeliac-specific antibody tests that detect antibodies directed against native or deamidated gliadin, such as AGA and anti-deamidated gliadin peptides (anti-DGP), or autoantibodies such as endomysial antibodies (EMA), and anti-tTG antibodies.[2,76,77] Most antibodies are typically of the IgA class and may be falsely negative in IgA-deficient patients with CD.[2,70,76,77] If the

clinical suspicion is high, then immunoglobulin G (IgG)-based tests, especially IgG-DGP, should be performed.[2,70,76,77]

Meta-analysis of a large number of studies on serological tests, both for adults and children, shows very high sensitivities and specificities for serological tests for celiac disease.[76,77,82] IgA-EMA is the most specific test (95–98%). The IgA-anti-tTG-2 and IgA-anti-DGP antibody tests both perform very well, at least in research settings, with sensitivity and specificity of 90–95% and 90–97%.[76,77,82] After the initial euphoric phase of very high sensitivities and specificities of anti-EMA ab and anti-tTG ab especially in the research setting, the data are now emerging that suggest sensitivity and specificity are not always high for these tests.[83,84] Calculations on the positive predictive value, when used on the general populations, show surprisingly low values for diagnosis of CD.[76] The lack of positive predictive value of the serological tests in the general population has raised concern about the overestimation of prevalence of CD.[84]

Point-of-care tests. Point-of-care tests are often referred to as "rapid tests" as they can be read immediately without the need to send serum to a laboratory. Tests recognizing antibodies against tTG-2 and DGP are available.[85,86] They are easy to use and may perform well.[85,86] However, concerns have been raised, especially if the reaction is "weak" that these tests may prompt some patients to start a GFD prior to receiving a proper diagnosis.

Which serological tests to perform? Because of their high sensitivity, high specificity, and ease of performance (ELISA-based test), anti-tTG testing is very popular and currently the first line test for screening patients suspected for CD.[69–72] A low titer of anti-tTGab has been described in several conditions unrelated to CD, such as other autoimmune diseases, infections, tumors, myocardial damage, liver disorders, and psoriasis.[76,77] These low level antibodies are not associated with the EMA positivity and hence are regarded as falsely positive.[69–72,76,77] This also explains why EMA has higher reliability for the diagnosis of CD.

Interpretation of serological tests. The cut-off values for a positive test vary widely among the available ELISA kits, and the numerical concentration of antibody obtained from one kit may not be comparable with that obtained by serological kit from another manufacturer.[70,83,87] This variability in the cut-off values makes clinical interpretation more challenging when sequential tests are done in patient follow up. Furthermore, there may be variability in the performance of ELISA kits within the batches of production and among the methods of performance.[70,76,77] The performance of a particular antibody test in a clinical setting depends on patient characteristics such as age, pretest probability, stage of the disease, and the ingested amounts of gluten.[70,76,77] These factors should be taken into account when interpreting positive and negative antibody results and establishing the optimal cut-off limits.

Validation of serological tests in different populations. The cut-off values for serological tests have mostly been derived from Western European populations.[70,75,76] The cut-off value for a positive test may vary from population to population, and there are no data on the normal cut-off values for the Asian population. Before these tests can be applied to the populations outside Western world, validation studies should be performed on an adequate sample of the population.

Relationship between serum concentrations of coeliac-specific antibodies and degree of villous atrophy. The presence of high titer of anti-tTG has been found to have a good correlation with the presence of villous atrophy.[88,89] In other words, the positive predictive value of high concentrations of anti-tTG (> 10 fold above the cut-off values) is very high for the presence of villous atrophy.[70]

Mucosal histological changes. The tissue damage in CD occurs due to the interaction between both innate and adaptive immune responses with immunogenic gliadin peptides.[90] Although CD is considered to be a multisystem disease, the small intestine is the primary organ involved and, therefore, demonstration of significant small intestinal villous damage is presently considered as essential for the diagnosis of CD.[36,70,71,90,91] The mucosal changes that are seen in patients with CD reflect the injury caused by the adaptive immune response to gliadin peptides but are not specific to CD.[90,91] Similar villous changes are observed in many other conditions such as tropical sprue, parasitic infection, Crohn's disease, and medications.[42,92,93] Furthermore, the degree of villous damage varies from the earliest lesion, such as intraepithelial lymphocytosis, to complete villous atrophy.[69,70,91,94]

Prerequisite for duodenal biopsies. Because histological changes in duodenal biopsies are dependent on the presence of gluten in the diet, it is best to ensure that biopsies are taken only if the patient is on a gluten-containing diet (equivalent to four slices of bread) for 2 to 6 weeks.[95] During the endoscopic procedure, the biopsies should be obtained along the length of the duodenum mostly from the post-ampullary area and should include at least one from the duodenal bulb, ensuring that at least four to six biopsies are taken in total.[95,96] Multiple biopsies are preferred because histological changes in CD may be patchy.[96] Specimens should ideally be labeled separately rather than bundled into one container. The fixative of choice for routine biopsies is 10% neutral buffered formalin using around ten times the volume of the specimens. All the interpretations regarding the villous height and crypt depth are dependent on properly oriented mucosal biopsy specimens. A biopsy is said to be properly oriented when at least three to four duodenal crypts are seen perpendicularly arranged on the thin bands of muscularis mucosae. Mounting biopsies on a piece of filter paper in the endoscopy room has been used to facilitate well-oriented sections, but there is no uniform practice; the view of some is that orientation can better be done by the pathologists than in endoscopic suites. For routine reporting of the histological changes, serial paraffin sections stained by HE are sufficient for making a diagnosis. Immunohistochemistry for intraepithelial lymphocytes (e.g. CD3 for T lymphocytes) may be performed in special situations such as nonresponse to GFD or on suspicion of refractory CD.[97]

Histological changes in duodenal mucosal biopsies are well characterized and accepted worldwide. Classifications of villous abnormalities are generally based on two factors—crypt-depth-villous-height (C : V) ratio and the density of intraepithelial

lymphocytic infiltration. The Modified Marsh classification is the most accepted way to describe villous abnormalities.[98]

As the pathological lesions in patients with CD are likely to be progressive with continued gluten ingestion, the C : V ratio may remain normal in early stages of the disease and the only feature present in the biopsies may be an increased density of intra-epithelial lymphocytes and/or crypt hypertrophy.[91,99] Flattening or atrophy of the villous and hyperplasia of crypts are the most severe mucosal villous changes.[91,98,100]

Recovery of mucosal abnormalities on GFD. While clinical manifestations improve within weeks of stopping gluten ingestion, the histological recovery takes longer (months to years) and might not recover completely in a substantial proportion of patients even after normalization of coeliac-specific serological tests.[101,102]

Genetic testing. Studies from the Western world suggest that 30–35% of the general population express CD-associated HLA genotypes.[103–106] More than 90% of CD patients express the HLA-DQ2.5 heterodimer encoded by the HLA-DQA1*05 (alpha-chain) and HLA-DQB1*02 (beta-chain) alleles, which may be inherited together on the same chromosome (*cis* configuration) or separately on the two homologous chromosomes (*trans* configuration).[103–106] Most of the remaining cases are HLA-DQ8 (DQA1*03 and DQB1*0302) positive.[103–106] In the small remaining population of CD patients that are neither DQ2.5 or DQ8, the patients typically express HLA-DQ molecules that contain "half" of DQ2.5 molecule as they are either DQ2.2 (DQA1*02:01, DQB1*02:01) or DQ7.5 (DQA1*05, DQB1*03:01).[103–106] Limited data from Asian nations suggest that *HLA-DQB1*02* is virtually absent from the Japanese population, but is present at low frequency in the Chinese population.[18,106] The few reports from the Middle East indicate that Iran, Saudi Arabia, and Turkey have a high frequency of *HLA-DQB1*02* and that A27-B8-DR3 is common in Turkish patients with CD.[104–106] In a study from Jordan, DQA1/B1 (0501; 0201) haplotype was present in 80% of patients and 66% of first-degree relatives compared with 32% of controls.[107] In Northern India, a high incidence of the A26-B8-DR3 (AH8.2) and Ax-B21-DR3 haplotypes has been reported in patients with CD.[108]

The utility of HLA testing as a screening test for CD is minimal because 30–35% of the general population in Western countries carry HLA-DQ2 and/or DQ8, but only a fraction of these individuals develop CD.[70–72] The high negative predictive value of HLA typing tests, however, indicates that absence of HLA-DQ2/DQ8 can exclude the possibility or future development of CD with a certainty close to 100%.[70–72,105,106] Clinical situations where HLA tests may be useful include an uncertain diagnosis of CD, difficulty getting patients currently on a GFD to resume gluten prior to serology and/or duodenal biopsy, Marsh I lesions in patients with negative coeliac-specific antibodies, or in children in whom there is a strong clinical suspicion of CD, high coeliac-specific antibodies are present and small-bowel biopsies are not going to be performed.[69–72] The test is especially useful for discriminating siblings who could be reassured about the unlikely chance of developing the disease from those who must be monitored for development of CD. HLA genes are lifelong stable markers and this positions this test uniquely so as to discriminate individuals genetically CD-susceptible or not susceptible before appearance of any clinical or serological signs.

Diagnostic criteria for CD

There is no single diagnostic test for CD. The diagnosis is made on the basis of several criteria, and these have evolved since the European Society of Pediatric Gastroenterology and Nutrition (ESPGHAN) presented the first diagnostic criteria in 1970.[109] These criteria required duodenal/jejunal biopsies to be done thrice for the diagnosis of CD—structurally abnormal intestinal mucosa when taking a diet containing gluten, clear improvement of villous architecture on GFD, and deterioration after rechallenge with gluten.[109] Such criteria were difficult to follow, and in 1989, they were modified such that a diagnosis of CD could be established by presence of typical clinical manifestations, villous atrophy, and unequivocal clinical response to GFD.[110]

With the improvement of the reliability and coeliac specificity of serological tests, and the good correlation between high concentrations of anti-tTG2ab (> 10 times upper limit of normal) and the presence of villous atrophy, ESPGHAN revised their guidelines for diagnosis of CD in 2012 to comprise the presence of coeliac-related symptoms, positive serology in high concentrations (> 10 fold above upper limit of normal), and the presence of HLA-DQ-2/DQ-8 haplotypes.[70] In such patients, biopsy for the demonstration of villous atrophy may not be essential. The diagnosis of CD is finally confirmed when the antibody levels decline on GFD preferably in association with a clinical response. However, the importance of duodenal histology was paramount when low or moderate anti-tTG2 levels were found and classical symptoms were lacking.[70]

Diagnostic criteria for CD may differ in Asia because of several factors. First, as discussed above, data on the basic characteristics such as the sensitivity and specificity of serological tests in Asia are not available. Secondly, Asia is a multiracial continent where dietary patterns vary widely and, therefore, the population-specific cut-offs may vary across different populations. Thirdly, while CD is the most common cause of villous atrophy in Caucasians, other causes, such as tropical sprue, parasitic infections, and immunoproliferative small intestinal diseases and combined variable immunodeficiency disease are more common in Asia.[51,92,93] Fourth, following a strict GFD is not easy in Asia because of relative unavailability of gluten-free food and inadvertent exposure. Hence, incomplete or no response in symptoms or serology to GFD should not necessarily raise suspicion about the validity of the basic diagnosis.

Management of CD

While there is little doubt that symptomatic patients diagnosed with CD should be treated with a GFD, whether *all* patients with CD need to be treated should be critically reviewed in light of the current information about clinical aspects and complications of CD considering the wide variability and heterogeneity of the disorder.[8,70–72] In this context, the vast majority of publications reporting about symptoms or long-term complications associated with CD are based on patients mostly having a symptomatic clinical course.[111] It should be kept in mind that the rate of diagnosed cases over the estimated total number of patients varies worldwide

between less of 5% to 30% (mostly symptomatic cases). In contrast, it seems very likely that at least 50% of patients with undiagnosed CD have a clinically silent course or even remain completely asymptomatic. The natural history of undiagnosed patients and the outcome of patients with subclinical CD require exploration before definitive conclusions can be established.

Having highlighted this important aspect, it must also be considered that a GFD has a significant impact on symptomatic patients, reverting symptoms very soon (mostly into the first 2 weeks) after starting on treatment.[112] A similar effect has been shown in the very few longitudinal studies that have examined aspects of quality-of-life and psychological distress of patients.[113] Thus, the most significant effect of treatment on symptoms and impaired quality-of-life parameters is produced during the first trimester after diagnosis and institution of treatment.[114] Furthermore, such improvement is parallel to the reduction of antibody concentrations and extent over the long-term in those strictly adherent to the diet.[115] In contrast, there is a paucity of studies on the effect of dietary treatment on the incidence of complications in the long term, but data are emerging to indicate the benefits of the GFD. For example, a recent longitudinal study has shown that diagnosis and treatment of CD reduces risk of bone fractures to the normal range.[116] High-quality longitudinal studies addressing issues suggested by cross-sectional studies, such as reduced survival and the increased risk of malignancies, are needed. *The balance of data strongly support serious consideration to active treatment of CD in all those diagnosed.*

The GFD. The principal treatment for CD is lifelong and complete avoidance of gluten in the diet.[70–72] Gluten is found in grains that contain prolamines from wheat or any Triticum species, such as spelt, durum wheat, rye, barley, oats, or their crossbred varieties.[117–119] Because of its viscoelastic properties, gluten is used extensively in the food and other industry, and may be found in many items used daily such as lipsticks, postage stamps, beer, ice creams, sweets, confectionary, tablets, and excipients.[117–119] Patients and their families require counseling and education in identifying gluten in foods to enable appropriate food choice to be made, and this would include skills in reading food labels (laws differ across the world), understanding of cross-contamination and hidden sources of gluten. It also requires instruction on how to eat away from home and how to maintain a nutritional adequate intake.[70–72,117–119] Most physicians would not possess sufficient knowledge or time to deliver such education. In most countries, dietitians and nutritionists with special knowledge in CD would do the teaching and the dietary follow-up.[117–119] The other essential ingredient is high-quality and comprehensive literature on gluten content of foods. This is now readily available on the internet and via patient advocacy groups in many countries.

The philosophy behind the GFD has varied across the world according to the strictness of what is considered "gluten-free."[120] In UK and some parts of Europe, a "limited detectable gluten diet" has been taught, in which minute amounts of gluten are permitted as defined by the recommendations of the Codex Alimentarius Commission. In 2012, the level of gluten in foods that could be considered gluten-free was redefined as 20 ppm (mg/kg), with "very low gluten" foods defined as those less than 100 ppm).[121] In Australia and New Zealand, a "no-detectable gluten" diet is taught.[120] This defines a gluten-free food as one in which gluten cannot be detected by the most sensitive validated assay and equates to about 2–5 ppm. This diet permits gluten-free wheat-derived ingredients to be consumed. In North America, a "zero-tolerance diet" is taught, in which only foods or ingredients from naturally gluten-free grains are permitted. Less strict definitions offer a wider choice of foods, while the more strict definitions favor a lower chance of gluten intake with better healing rates and symptom control.

The safe limit of gluten intake varies across patients and has been considered to be 10–100 mg/day[122,123] although a subsequent study indicated that the upper limit should closer to more like 50 mg/day.[124] These are indeed minute amounts when, for example, the average gluten intake in the West varies from 10–20 g/day[125] and a typical North Indian diet, where flat bread is customary, contains 5–30 g gluten per day.

A key to the success of the GFD is compliance.[70–72,117,118] Four methods for assessment of adherence to the GFD have been applied. Dietitian-led evaluation by direct history taking, food records, and cross-check questioning is very useful in skilled hands.[117,118] Self-reported questionnaires have been developed.[126,127] These are probably more useful for epidemiological studies rather than for individual patient management. Coeliac serology can be useful, but falling concentrations of coeliac-specific antibodies indicate gluten reduction and have limited ability to define complete adherence.[128] Once the antibodies have normalized, subsequent increase in levels is considered a good indicator of gluten ingestion. The ultimate measure of adherence is the demonstration of intestinal healing, but this may not occur even in patients with strict gluten avoidance.[129,130] Studies of the success of adherence have all been performed in Western countries, where risk factors for non-adherence include lower level of education, non-affluence, psychological issues, diagnosis in childhood, oligosymptomatic CD, not being a member of an advocacy group, not having regular dietitian follow-up and, in UK, being of an ethnic minority group such as South Asian.[131–133]

Monitoring response to treatment. Four targets of therapy have been proposed. The traditional target—*relief of symptoms*—is readily assessable and important, especially because symptom avoidance is a major motivation for adherence to the GFD and is directly related to quality of life.[134] However, symptoms are a poor guide to intestinal mucosal healing, may not be directly related to the CD, and increasing numbers of patients are oligosymptomatic at diagnosis. The second target is *correction of nutritional deficiencies*. This is of paramount importance in children because physical growth, rapid catch–up in height, and normalization of body mass index is associated with institution of the GFD in a child with newly diagnosed CD.[70–72] The third potential target is to *normalize immunological abnormalities*. The only immunological tests currently available are coeliac-specific serological assessment. Unfortunately, there is poor correlation between normalization of serology and intestinal healing.[135] The final target is to achieve *mucosal healing*, which is an excellent surrogate for correction of immunological activation and is associated with improved outcomes in terms of morbidity and mortality. There is no consensus on the definition of mucosal healing as to whether it refers to complete mucosal healing or just normalization of

crypt-villous ratios (so-called mucosal recovery). Such a target would require an index diagnostic biopsy to permit assessment of improvement. The problems with mucosal healing as the goal of therapy include that its assessment requires duodenal biopsy and expert histopathological evaluation, and that it is achieved in a minority of adults although it is usual in children.[101,102] If mucosal healing is the ultimate target of therapy, then duodenal biopsies should be performed regularly (e.g. yearly) until healing is achieved. This is not commonly practiced, although it is part of the Cambridge pathway that has recently been presented.[136] The role of repeat biopsy is unclear. It is not recommended in the most recent WGO guidelines.[71] Its place in management strategies in Asia has not been studied.

Failure to respond to a GFD is usually due to a lack of adherence to the diet or to inadvertent intake of gluten. However, refractory CD (RCD) is defined as histopathological abnormalities that persist (or recur) in association with clinical symptoms despite excellent adherence to GFD for at least 12 months.[137,138] Its true prevalence is uncertain but may affect up to 5% of patients.[137,138] There are two types of RCD (RCD I and RCD II), which are differentiated by the proportion of aberrant intraepithelial lymphocytes on flow cytometry and by prognosis. RCD is discussed in detail in recent reviews.[137,138]

Specific issues for CD in the Asia–Pacific region

Epidemiology: under-recognition of coeliac disease. The available data suggest that CD is much more common in some areas of the Asia–Pacific region than previously appreciated.[9,10,18,37] However, CD is not recognized in many Asian nations, and even in nations where CD is recognized, only the most apparent patients are being diagnosed. In India alone, almost 4–6 million are expected to have CD and only a few thousands have been diagnosed until now.[9,10,33,34] The foremost among the possible explanations for under-diagnosis of CD and/or unavailability of serological tests is the mistaken belief that CD is rare/uncommon in this part of the world. Just an increased awareness about the disease, its wide clinical spectrum and the availability of highly sensitive and specific serologic tests has led to an increase in recognition of CD in some Asian nations. It is also possible that the recent increase in the prevalence of CD in some Asian nations is because of the widespread diffusion of Western dietary habits, thus increasing consumption of gluten-containing cereals.

Dietary practices and genetic diversities are the two most important reasons for variations in the prevalence of CD in Asian countries. While rice is staple cereal in many Asian nations, there has been a change in dietary behavior with wheat and wheat products being included in their diet. In India, CD is currently been identified more commonly in the Northern part than in the Southern part of the country.[30,31] Wheat is staple food in some of States in Northern part of India, while rice remains staple cereal in Southern States of India.[30,31] In China where CD is thought to be an uncommon disease, food-containing gluten, such as noodles, steamed bread, kaofu, and dumplings, is increasingly used. The question arises why CD is uncommon in China despite the rates of gluten ingestion. Perhaps the Chinese are protected from CD because of their genetic makeup.

How to increase recognition of CD in the Asia–Pacific region. There are three broad strategies to increase recognition of CD in this region.

- *Establish the prevalence of CD across the region:* While population-based studies are ideal for estimating the prevalence of CD in a particular country/region, this is labor intensive and expensive. An alternative is conducting pilot studies to estimate the prevalence of CD in some of the high-risk patient groups, for instance patients with type 1 diabetes, chronic diarrhea, anemia, or short stature where prevalence of CD is several fold higher than for the general population. If the existence of CD is confirmed by these pilot studies, population-based studies can be conducted. Furthermore, a multicenter epidemiological effort aimed to measure the relevant parameters (level of gluten intake, frequency, and pattern of CD-predisposing genotypes) could help clarify the complex interplay between genetic and environmental factors leading to CD development.
- *Education:* It is essential that awareness of and knowledge about CD and its disease associations increase in medical practitioners. The obvious groups to target are pediatricians, family physicians, gastroenterologists, and histopathologists. However, it should be emphasized that CD may report to other medical specialists such as endocrinologists where patients present with short stature or type I diabetes, to hematologists with anemia, to rheumatologists with metabolic bone diseases, and to gynecologists with delay in menarche, secondary amenorrhea, or infertility.

  Currently, a due emphasis is not placed on CD in the undergraduate and postgraduate medical curriculum. In the majority of the undergraduate and postgraduate textbooks of medicine, CD is generally dealt with in the chapters on malabsorption and only limited information about CD is provided. A due emphasis should be put on CD during undergraduate and postgraduate medical education. Furthermore, a constant reminder should be provided to physicians, internists, gastroenterologists, hematologists, and endocrinologists through continuing medical education programs.

  Generally, primary care physicians and family physicians are the first contact of patients with CD. Therefore, empowering primary care and family physicians should play key role in increasing the detection of CD. Gastroenterologists in Asian countries can play a key role in increasing the awareness in their own countries about CD. Very often histopathologists are not conversant with the handling and reporting of mucosal biopsies from patients suspected to have CD. While specialist gastrointestinal pathologists may be consulted or slides sent for review, it is necessary for all pathologists to be trained in handling such biopsies and at least providing a preliminary report to the attending physician. With the estimated prevalence of CD in this Asia–Pacific region, it is very unlikely that there would be a commensurate increase in gastrointestinal pathologists. Hence, general histopathologists in these countries would screen biopsies and referrals would be limited to difficult cases. Furthermore, histopathologists would be required to train and supervise technical staff handling such specimens. This could be done by ensuring appropriate training during residency, postgraduation and fellowships, and through continuing medical educational programs. Similarly, awareness should be created and adequate

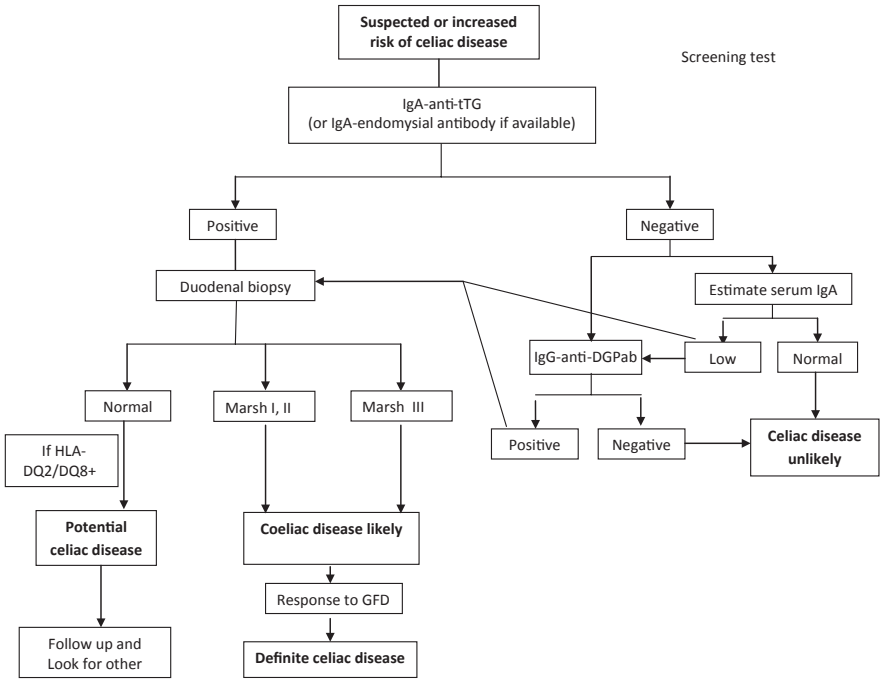

Figure 1 Detailed algorithm of the diagnosis of CD. GFD, gluten free diet; HLA, human leukocyte antigen; IgA, immunoglobulin A; IgA-anti-DGP, immunoglobulin A anti-deamidated gliadin peptides; IgA-anti-tTGab, immunoglobulin A anti-transglutaminase antibodies.

training should be provided to technical staff in handling and properly orienting biopsies prior to cutting the sections of the biopsies.

- *Increased funding:* Government and nongovernmental funding agencies should prioritize and allocate funds for research (epidemiological and basic research) on CD. Furthermore, funding to make serological tests more readily accessible will promote their use (see below).

Issues regarding presentation of CD. Awareness of the protean manifestations and presentations of CD, particularly the so-called atypical ones, is a major issue facing the Asia–Pacific region. It compounds the lack of awareness of the disease itself within the population. A high degree of clinical suspicion is important for diagnosis of CD because manifestations of CD vary widely and are not limited to the intestine.[45–48] Education of the medical communities across wide variety of specialties as well as during medical training, as discussed above, is required.

Diagnostic issues. Making a diagnosis of CD requires clinical suspicion usually followed by performance of a screening serological test followed by diagnostic histological assessment of the duodenal mucosa. Both serology and histopathology have challenges for the Asia–Pacific populations.

- *Serology:* Currently, most coeliac-specific serological assay kits in Asia are imported from Europe. Their diagnostic cut-off values of antibody concentrations have been determined based on Caucasian populations. With the difference and diversity in gluten ingestion and genetic background, the cut-off values for a positive test in Asia may not be similar to those reported in the Caucasians. Therefore, there is a real need for the estimation of population-specific cut-off values of serological tests especially for anti-tTG and anti-DGP. The other diagnostic aspects of serological tests such as specificity, sensitivity, positive predictive values, and negative predictive values should also be determined in Asian populations.
- *Histopathology:* Because of the occurrence of tropical enteropathy, small intestinal villi may be shorter in people from many Asian countries. Furthermore, there is lack of normative data on the C : V ratio and normal intraepithelial lymphocyte counts per 100 enterocytes, both of which are critical for making a diagnosis. There is a need to define the cut-off values that identify intraepithelial lymphocytosis.

A firm diagnosis of CD should be made before initiating GFD in Asia because CD is a lifelong disease that requires lifelong therapy with a diet that is challenging. Furthermore, making a diagnosis of CD in patients already following a GFD has issues because serological and histological criteria depend upon the presence of pathogenic events related to gluten ingestion. On current data, anti-tTG-2 is the preferred screening test in those suspected to have CD.[70–72] In those who are IgA deficient, an IgG-based test is needed and anti-DGP seems to perform the best, at least in Caucasian populations. It is inappropriate to rely only upon serology for diagnosis, especially with the uncertainties regarding interpretation of serological tests in Asian populations. Hence, duodenal biopsies, including several biopsies of the first and second/third parts of the duodenum, are essential to secure the diagnosis. A more detailed algorithm of the diagnosis of CD is illustrated in Figure 1.

Management issues. As for Western countries, lifelong adherence to a GFD is the cornerstone of successful management. There are three major impediments to the successful use of a GFD across many Asian countries.

- *The need for expert dietitians:* Management of CD is very different from that of other gastrointestinal diseases in that the core of the treatment is dietary and non-medicinal.[117,118] Prescribing GFD after diagnosis is easy, but its institution and maintenance of adherence pose the real challenges. Most physicians may not have enough expertise in counseling for GFD. In Western countries, dietitians play a pivotal role in the management of patients with CD. However, there is a lack of trained dietitians in most Asian nations; and even if they are there, most do not have sufficient expertise in the management of CD.
- *The need for gluten-free infrastructure in the food supply:* At present, there is neither an organized sector nor industry for gluten-free products in Asia, and gluten-free food products are not readily available. Gluten is ubiquitous in the food industry and often used in a variety of food items. More importantly, there is no gluten labeling in the available food products. The patient cannot judge the safety of an over-the-counter food product. There is an urgent need for legislation to enforce gluten labeling of the marketed food products.
- *The lack of patient advocacy organizations:* The importance of excellent written information in local language and with relevance to the local food supply cannot be overstated. This has been facilitated in many countries by patient advocacy organizations. They have also provided a collective voice for patients to exert political pressure.

The nature and structure of follow-up once a diagnosis is made is undergoing much discussion in Western countries and consensus as to the targets for treatment—particularly whether they should be only symptoms or include mucosal healing—has yet to be reached. In the Asia–Pacific, the problems are compounded by issues associated with inadequate medical infrastructure and funding. The lack of expert dietitians compounds excellence in assessment of adherence and correction of dietary issues. Endoscopic evaluation in follow-up is not possible in many settings principally because of lack of availability and prioritization. Nevertheless, it is highly recommended that follow-up occur and these less available resources are applied at least if symptoms or nutritional problems are not being resolved by treatment with the GFD.

Conclusions

Although the absolute number of patients with CD at present is not very large, this number is expected to increase markedly over the next few years/decades because of heightened awareness and increased diagnosis. It is now that the medical community across the Asia–Pacific region should be properly defining the extent of the problem and be preparing to handle the impending epidemic of CD.

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