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**Celiac disease in Asia beyond Middle East and Indian subcontinent: Epidemiological burden and diagnostic barriers**

Poddighe D *et al*. Celiac disease in Asia

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**Abstract**

Celiac disease (CD) had been considered uncommon in Asia for a long time. However, several studies suggested that, in the Indian subcontinent and Middle East countries, CD is present and as prevalent as in Western countries. Outside these Asian regions, the information about the epidemiology of CD is still lacking or largely incomplete, because of different and variable reasons. Here, we discuss the epidemiological aspects and the diagnostic barriers in the following Asian regions: China, Japan, South-East Asia and Russia/Central Asia. In some of these regions (and in Russian and Central Asia, particularly), the prevalence of CD is very likely to be underestimated. Several factors may variably contribute to hamper this diagnosis (and, thus, the estimation of its epidemiological burden), including poor disease awareness among physicians and/or patients, limited access to diagnostic resources, inappropriate use or interpretation of the serological tests, absence of standardized diagnostic and endoscopic protocols and insufficient expertise in the histopathological interpretation.

**Key Words:** Celiac disease; Epidemiology; Prevalence; Asia; China; Japan; Russia; Central Asia; HLA-DQB1; Diagnostic barriers

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**Core Tip:** This editorial discusses the main epidemiological aspects of celiac disease in Asia, outside the Indian subcontinent and Middle East countries. Indeed, the information about the epidemiology of celiac disease is still lacking or largely incomplete in those other Asian regions, where the disease prevalence is likely be underestimated in some of those. Additionally, the potential factors contributing to the diagnostic difficulties in these Asian regions (China, Japan, South-East Asia and Russia/Centra Asia) are discussed.

**INTRODUCTION**

The global prevalence of celiac disease (CD) is estimated to be around 1% in the general population. However, this estimation is based on epidemiological studies that mainly come from the European and (South and North) American continents[1,2]. Conversely, CD had been considered to be uncommon in Asia for a long time, but several studies in the previous two decades demonstrated that CD is present and, in the Indian subcontinent and in the Middle East, it is as prevalent as in Western countries[3-5].

A few years ago, the meta-analysis by Singh *et al*[6] reported that the pooled prevalence of CD in Asia was around 0.5% without any significant difference between children and adults: except for one study from Malaysia, all the clinical studies were from the Middle East (Turkey, *n* = 5; Iran, *n* = 4; Israel, *n* = 2; Saudi Arabia, *n* = 2; Jordan, *n* = 1) and India (*n* = 3). Actually, some authors recently estimated that CD prevalence may be as high as 1% even in these Asian countries, based on the assessment of the HLA-DQB1\*02 allelic frequencies and wheat consumption in the general population[7]. Indeed, the HLA-DQB1\*02 allelic variant is the major HLA-related CD predisposing allele as well as gluten dietary intake is the necessary environmental trigger of the immunopathological process underlying CD[8,9]. In India, this estimation has found confirmation in the community-based study by Makharia *et al*[10], who demonstrated a CD prevalence of 1.04% in the northern part of India, where both the dietary style and *HLA-DQ* genetic background are more favorable to the development of CD. A study from Iran, including 1500 healthy school children serologically screened for CD, led to the diagnosis of biopsy proven CD in 0.6% of this pediatric cohort; most of them were apparently silent cases and, therefore, it is reasonable to expect a higher prevalence in the general population[11]. Similar considerations may be done about Turkey, whereby Tatar *et al*[12] screened 2000 healthy blood donors for CD markers: 1.3% (*n* = 26) resulted to be positive and 12 donors (0.6%) were diagnosed with CD after biopsy; again, considering that most part of these serologically positive donors (*n* = 14) could not be contacted or refused the endoscopy and all these diagnosed cases were silent forms, the overall prevalence is supposed to be greater.

Outside the aforementioned Asian regions, the information about CD epidemiology is still lacking or largely incomplete, because of different and variable reasons. For the purpose of the present discussion, the following Asian regions are considered separately: China, Japan, South-East Asia, Russia/Central Asia.

**CHINA**

Among the aforementioned Asian regions, China is the region where more clinical studies on CD have been published in the last decade. In 2011, Wang *et al*[13] published a national multicentric study describing 14 Chinese children histologically diagnosed with CD after serological screening because of chronic diarrhea. Moreover, Yuan *et al*[14] reported that the presence of DQB1\*0201 allele was not negligible in the Chinese population: overall, the frequency of this allele was 10.5% and the highest values were described in the north-western part of China, where non-Chinese ethnic minorities are mainly settled and the HLA-DQB1\*02 allelic frequencies are > 20%-25% (*e.g.*, Kazakh and Uygur ethnicities).Recently, the same authors reported a 2.19% rate of CD seropositivity in a cross-sectional study including 19778 Chinese adolescents and young adults[15].

The dietary exposure to gluten has increased over the past 50 years in the Chinese population, since wheat is currently the second staple food (after rice) in China, which is one of the largest producers and consumers of wheat (especially in the northern area) worldwide. Therefore, CD is an emerging disease in this country and, despite the lack of epidemiological studies with a complete diagnostic definition, the awareness of this disease and its potential impact on health should be raised in such a large population[14]. Very recently, Chen and Li[16] discussed this aspect. In addition to the submerged epidemiological burden of CD in China, due to the poor awareness among the population and health professionals, these authors also reported some limitations in the diagnostic approach, since the standardized tissue acquisition and the histological description are still problematic in some local and less resourced settings. Accordingly, they emphasized that, in most studies, seropositive individuals could not undergo the duodenal biopsy needed for the confirmation of CD diagnosis.

**JAPAN**

In Japan, the epidemiological burden of CD is still extremely low. In 2018, Fukunaga *et al*[17] described only 2 biopsy-based CD diagnoses among 2055 people (including 2008 asymptomatic individuals and 47 adults complaining of chronic abdominal symptoms), which corresponds to < 0.1% prevalence. This finding is consistent with the very low frequency of the HLA-DQ2/DQ8 immunotype. Indeed, in a study including 371 unrelated healthy apheresis blood donors, the HLA-DQB1\*02 allelic frequency was reported to be < 1%, even though the DQB1\*03:02 allele was relatively common (10.8%)[18]. Moreover, although the dietary exposure to gluten has been increasing even in Japan, here the consumption of wheat is still relatively low (approximately, one-third of that estimated in Western countries)[17].

The same research group reported a positive CD serological rate [based on anti-tissue transglutaminase (tTG) immunoglobulin (Ig) A antibody] of 0.19% in 2005 Japanese adults (study period: 2008-2013), which is consistent with their aforementioned study (study period: 2014-2016), where the positivity rate was 0.2% (based on the 10 U/mL titer cut-off)[17,19]. Accordingly, these authors observed that, in the Japanese clinical practice, CD is rarely considered by physicians, when they are called to manage patients with chronic abdominal symptoms[17].

However, it must be emphasized that the available studies were mostly, if not completely, focused on asymptomatic/healthy people and, thus, the actual prevalence of CD seropositivity and diagnosis may be a little higher than that reported so far. However, Hokari and Higashiyama[20] observed that Japanese physicians are unlikely to overlook CD, since the endoscopic assessment is well-established in Japan for patients complaining of chronic abdominal symptoms, this procedure is performed by well-trained endoscopists and the histopathological appearance of CD mucosa is well-known.

Therefore, the low epidemiological burden of CD in Japan is considered to be real: It is consistent with the immunogenetic background and the dietary style, and there are no major diagnostic barriers. However, this situation may change in the next future if the wheat consumption increases.

**SOUTH-EAST ASIA**

A few clinical studies assessed the epidemiological burden of CD in this Asian region[21]. In most countries of South-East Asia, the frequency of HLA-DQB1\*02 is estimated to be < 10%-15%[6]. Anyway, the low dietary intake of gluten also contributes to the scarce prevalence of CD.

In Vietnam, the CD autoimmunity was assessed in 1961 children: around 1% resulted positive for anti-tTG IgA[22]. In Thailand, the CD serology was assessed in 46 children with type 1 diabetes mellitus: only one resulted positive for anti-tTG IgA and, considering an expected prevalence greater than 5% (and up to 10%) in such a risk group, the prevalence of CD is supposed to be low in Thai children, in terms of general population[23,24].

In Malaysia, Yap *et al*[25] reported a relatively high CD seroprevalence (1.25%) in healthy young adults. This finding may be explained by the fact that the Malaysian population includes three main ethnicities (Malay, Chinese, and Indian), but the HLA genotyping was not performed in this study. However, these authors showed that CD is underdiagnosed in this country and discussed the potential explanations. Indeed, the poor medical awareness of CD (and, thus, the low request rate of CD serology tests), the use of less sensitive CD serological markers, the inappropriate application of endoscopic protocols and the under-recognition of milder CD histopathological patterns, were all considered to be contributing factors.

**RUSSIA AND CENTRAL ASIA**

The review by Savvateeva *et al*[26] is still the main source providing an overall and indirect epidemiological picture of CD in Russia, as regards the international and English medical literature. Here, most studies (study periods: From 2000 to 2014; Russian language) included mainly children: These authors concluded that the pediatric CD prevalence in this country has been increasing in the last few decades and, currently, it may arrive at least up to 0.6%, although significant inter-regional variations should be considered, due to the wide geographical extension of this country. Indeed, the carrier frequency of HLA-DQ2/DQ8 haplotypes in the Russian population (especially in the Western part) seems to be comparable to that in Europe. Thus, although these authors suggested an epidemiological trend and prevalence rates similar to Europe, there is no discussion on the potential barriers hampering CD diagnosis in this country; conversely, they mentioned a well-established therapeutical support and follow-up protocols for CD patients in Russia.

In this review, some epidemiological data from Central Asia and, in detail, from Kazakhstan are indirectly described: a CD prevalence of 1:262 children (< 0.4%) was reported in this country; however, the diagnostic approach (based on anti-gliadin antibodies) and the study design used for this evaluation, were prone to a significant underestimation of the actual prevalence[21,26]. Moreover, our group recently showed that the carrier frequencies of HLA-DQB1\*02 and HLA-DQB1\*03:02 in Kazakhstani healthy blood donors are respectively 38% and 12.5% and, thus, are comparable to the values of the Caucasian populations. Therefore, considering the high consumption of wheat foods in the Kazakhstani population, we concluded that it is reasonable to expect that the CD prevalence in Kazakhstan may be remarkable and comparable to that reported in Europe[27].

Therefore, large and well-designed clinical studies are needed to provide a reliable estimation of the CD epidemiological burden in Central Asia. However, CD is very likely to be underdiagnosed in Kazakhstan. Indeed, several barriers currently contribute to hamper the achievement of CD diagnosis in this country, including the inappropriate use of the serological tests, the limited access to these investigations for economic reasons, the absence of standardized protocols for the endoscopic procedures and the difficulties in the histopathological interpretation[27,28]. All these aspects are linked like chain rings that are joined each other and, finally, lead to the under-estimation of CD diagnostic and epidemiological burden in this country, as graphically summarized in Figure 1. These considerations might be also applied to other regions of Central Asia, where the economic resources are even lower.

**CONCLUSION**

Outside the Indian subcontinent and Middle East countries, the epidemiological burden of CD in Asia is underestimated, especially in Russian and Central Asia, where wheat is a staple food and the genetic predisposition to CD is comparable to Europe.

In agreement with other authors[29,30], our discussion evidenced several factors that variably (according to different Asian countries and regions) contribute to hamper the CD diagnosis and, thus, to estimate its epidemiological burden, such as poor disease awareness among physicians and/or patients, limited access to diagnostic resources (because of economic and/or organizational and/or geographical reasons), inappropriate use or interpretation of the available serological tests, absence of standardized diagnostic and endoscopic protocols and, finally, insufficient expertise in the histopathological interpretation.

**REFERENCES**

1 **Lindfors K**, Ciacci C, Kurppa K, Lundin KEA, Makharia GK, Mearin ML, Murray JA, Verdu EF, Kaukinen K. Coeliac disease. *Nat Rev Dis Primers* 2019; **5**: 3 [PMID: 30631077 DOI: 10.1038/s41572-018-0054-z]

2 **Lebwohl B**, Sanders DS, Green PHR. Coeliac disease. *Lancet* 2018; **391**: 70-81 [PMID: 28760445 DOI: 10.1016/S0140-6736(17)31796-8]

3 **Ashtari S**, Pourhoseingholi MA, Rostami K, Aghdaei HA, Rostami-Nejad M, Busani L, Tavirani MR, Zali MR. Prevalence of gluten-related disorders in Asia-Pacific region: a systematic review. *J Gastrointestin Liver Dis* 2019; **28**: 95-105 [PMID: 30851178 DOI: 10.15403/jgld.2014.1121.281.sys]

4 **Cummins AG**, Roberts-Thomson IC. Prevalence of celiac disease in the Asia-Pacific region. *J Gastroenterol Hepatol* 2009; **24**: 1347-1351 [PMID: 19702902 DOI: 10.1111/j.1440-1746.2009.05932.x]

5 **Comba A**, Eren NB, Demir E. Prevalence of celiac disease among school-age children in Çorum, Turkey. *Turk J Gastroenterol* 2018; **29**: 595-600 [PMID: 30260783 DOI: 10.5152/tjg.2018.18020]

6 **Singh P**, Arora S, Singh A, Strand TA, Makharia GK. Prevalence of celiac disease in Asia: A systematic review and meta-analysis. *J Gastroenterol Hepatol* 2016; **31**: 1095-1101 [PMID: 26678020 DOI: 10.1111/jgh.13270]

7 **Makharia GK**, Catassi C. Celiac Disease in Asia. *Gastroenterol Clin North Am* 2019; **48**: 101-113 [PMID: 30711203 DOI: 10.1016/j.gtc.2018.09.007]

8 **Poddighe D**, Rebuffi C, De Silvestri A, Capittini C. Carrier frequency of HLA-DQB1\*02 allele in patients affected with celiac disease: A systematic review assessing the potential rationale of a targeted allelic genotyping as a first-line screening. *World J Gastroenterol* 2020; **26**: 1365-1381 [PMID: 32256023 DOI: 10.3748/wjg.v26.i12.1365]

9 **Megiorni F**, Mora B, Bonamico M, Barbato M, Nenna R, Maiella G, Lulli P, Mazzilli MC. HLA-DQ and risk gradient for celiac disease. *Hum Immunol* 2009; **70**: 55-59 [PMID: 19027045 DOI: 10.1016/j.humimm.2008.10.018]

10 **Makharia GK**, Verma AK, Amarchand R, Bhatnagar S, Das P, Goswami A, Bhatia V, Ahuja V, Datta Gupta S, Anand K. Prevalence of celiac disease in the northern part of India: a community based study. *J Gastroenterol Hepatol* 2011; **26**: 894-900 [PMID: 21182543 DOI: 10.1111/j.1440-1746.2010.06606.x]

11 **Dehghani SM**, Haghighat M, Mobayen A, Rezaianzadeh A, Geramizadeh B. Prevalence of celiac disease in healthy Iranian school children. *Ann Saudi Med* 2013; **33**: 159-161 [PMID: 23563005 DOI: 10.5144/0256-4947.2013.159]

12 **Tatar G**, Elsurer R, Simsek H, Balaban YH, Hascelik G, Ozcebe OI, Buyukasik Y, Sokmensuer C. Screening of tissue transglutaminase antibody in healthy blood donors for celiac disease screening in the Turkish population. *Dig Dis Sci* 2004; **49**: 1479-1484 [PMID: 15481323 DOI: 10.1023/b:ddas.0000042250.59327.91]

13 **Wang XQ**, Liu W, Xu CD, Mei H, Gao Y, Peng HM, Yuan L, Xu JJ. Celiac disease in children with diarrhea in 4 cities in China. *J Pediatr Gastroenterol Nutr* 2011; **53**: 368-370 [PMID: 21701402 DOI: 10.1097/MPG.0b013e31822a0128]

14 **Yuan J**, Gao J, Li X, Liu F, Wijmenga C, Chen H, Gilissen LJ. The tip of the "celiac iceberg" in China: a systematic review and meta-analysis. *PLoS One* 2013; **8**: e81151 [PMID: 24324669 DOI: 10.1371/journal.pone.0081151]

15 **Yuan J**, Zhou C, Gao J, Li J, Yu F, Lu J, Li X, Wang X, Tong P, Wu Z, Yang A, Yao Y, Nadif S, Shu H, Jiang X, Wu Y, Gilissen L, Chen H. Prevalence of Celiac Disease Autoimmunity Among Adolescents and Young Adults in China. *Clin Gastroenterol Hepatol* 2017; **15**: 1572-1579.e1 [PMID: 28433781 DOI: 10.1016/j.cgh.2017.04.025]

16 **Chen CY**, Li JN. Insufficient awareness of celiac disease in China: population-based screening is needed. *Chin Med J (Engl)* 2019; **132**: 1513-1515 [PMID: 31188159 DOI: 10.1097/CM9.0000000000000305]

17 **Fukunaga M**, Ishimura N, Fukuyama C, Izumi D, Ishikawa N, Araki A, Oka A, Mishiro T, Ishihara S, Maruyama R, Adachi K, Kinoshita Y. Celiac disease in non-clinical populations of Japan. *J Gastroenterol* 2018; **53**: 208-214 [PMID: 28389733 DOI: 10.1007/s00535-017-1339-9]

18 **Saito S**, Ota S, Yamada E, Inoko H, Ota M. Allele frequencies and haplotypic associations defined by allelic DNA typing at HLA class I and class II loci in the Japanese population. *Tissue Antigens* 2000; **56**: 522-529 [PMID: 11169242 DOI: 10.1034/j.1399-0039.2000.560606.x]

19 **Fukunaga M**, Ishimura N, Abe T, Takeda M, Isomura M, Kinoshita Y, Ishihara S. Serological screening for celiac disease in adults in Japan: Shimane CoHRE study. *JGH Open* 2020; **4**: 558-560 [PMID: 32782937 DOI: 10.1002/jgh3.12334]

20 **Hokari R**, Higashiyama M. Extremely low prevalence of Celiac disease in Japan: Eternal silence or just the calm before the storm? *JGH Open* 2020; **4**: 554-555 [PMID: 32782935 DOI: 10.1002/jgh3.12352]

21 **Poddighe D**, Rakhimzhanova M, Marchenko Y, Catassi C. Pediatric Celiac Disease in Central and East Asia: Current Knowledge and Prevalence. *Medicina (Kaunas)* 2019; **55** [PMID: 30642036 DOI: 10.3390/medicina55010011]

22 **Zanella S**, De Leo L, Nguyen-Ngoc-Quynh L, Nguyen-Duy B, Not T, Tran-Thi-Chi M, Phung-Duc S, Le-Thanh H, Malaventura C, Vatta S, Ziberna F, Mazzocco M, Volpato S, Phung-Tuyet L, Le-Thi-Minh H, Borgna-Pignatti C. Cross-sectional study of coeliac autoimmunity in a population of Vietnamese children. *BMJ Open* 2016; **6**: e011173 [PMID: 27329441 DOI: 10.1136/bmjopen-2016-011173]

23 **Thammarakcharoen T**, Hirankarn N, Sahakitrungruang T, Thongmee T, Kuptawintu P, Kanoonthong S, Chongsrisawat V. Frequency of HLA-DQB1\*0201/02 and DQB1\*0302 alleles and tissue transglutaminase antibody seropositivity in children with type 1 diabetes mellitus. *Asian Pac J Allergy Immunol* 2017; **35**: 82-85 [PMID: 27543737 DOI: 10.12932/AP0751]

24 **Pham-Short A**, Donaghue KC, Ambler G, Phelan H, Twigg S, Craig ME. Screening for Celiac Disease in Type 1 Diabetes: A Systematic Review. *Pediatrics* 2015; **136**: e170-e176 [PMID: 26077482 DOI: 10.1542/peds.2014-2883]

25 **Yap TW**, Chan WK, Leow AH, Azmi AN, Loke MF, Vadivelu J, Goh KL. Prevalence of serum celiac antibodies in a multiracial Asian population--a first study in the young Asian adult population of Malaysia. *PLoS One* 2015; **10**: e0121908 [PMID: 25799401 DOI: 10.1371/journal.pone.0121908]

26 **Savvateeva LV**, Erdes SI, Antishin AS, Zamyatnin AA Jr. Overview of Celiac Disease in Russia: Regional Data and Estimated Prevalence. *J Immunol Res* 2017; **2017**: 2314813 [PMID: 28316996 DOI: 10.1155/2017/2314813]

27 **Poddighe D**, Turganbekova A, Baymukasheva D, Saduakas Z, Zhanzakova Z, Abdrakhmanova S. Genetic predisposition to celiac disease in Kazakhstan: Potential impact on the clinical practice in Central Asia. *PLoS One* 2020; **15**: e0226546 [PMID: 31895924 DOI: 10.1371/journal.pone.0226546]

28 **Penny HA**, Raju SA, Lau MS, Marks LJ, Baggus EM, Bai JC, Bassotti G, Bontkes HJ, Carroccio A, Danciu M, Derakhshan MH, Ensari A, Ganji A, Green PHR, Johnson MW, Ishaq S, Lebwohl B, Levene A, Maxim R, Mohaghegh Shalmani H, Rostami-Nejad M, Rowlands D, Spiridon IA, Srivastava A, Volta U, Villanacci V, Wild G, Cross SS, Rostami K, Sanders DS. Accuracy of a no-biopsy approach for the diagnosis of coeliac disease across different adult cohorts. *Gut* 2020 [PMID: 33139268 DOI: 10.1136/gutjnl-2020-320913]

29 **Agarwal A**, Chauhan A, Ahuja V, Makharia GK. Opportunities and challenges in the management of celiac disease in Asia. *JGH Open* 2020; **4**: 795-799 [PMID: 33102747 DOI: 10.1002/jgh3.12381]

30 **Dhawan A**, Agarwal A, Mulder CJ, Makharia GK. Celiac disease in the East and the West: Bridging the gaps between the guidelines and their implementation in daily practice is mandatory. *Indian J Gastroenterol* 2019; **38**: 185-189 [PMID: 31313236 DOI: 10.1007/s12664-019-00970-7]

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**Figure Legends**



**Figure 1 Schematic overview of the diagnostic barriers in Kazakhstan.** CD: Celiac disease.