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Prevalence of celiac disease in the northern part of India: A community based study

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Abstract

Background and Aim: While celiac disease is estimated to affect about 1% of the world's population, it is thought to be uncommon not only in India but in Asia also. There is a lack of studies on the prevalence of celiac disease from Asian nations. The aim of the present study was to estimate the prevalence of celiac disease in the community.

Methods: In a cross sectional study, we estimated the prevalence of celiac disease in urban and rural populations in the National Capital Region, Delhi, India. A structured questionnaire was administered, by door-to-door visits, to all participants to collect socio-demographic data and to screen for features of celiac disease, namely chronic or recurrent diarrhea and, anemia. In children, additional features, namely short stature (linear height below 5th percentile for age) and failure to thrive/gain weight were also used. All respondents who were screen positive (any one of above) and 10% of screen negative individuals were called for serological testing, which is anti-tissue transglutaminase antibody. All serologically positive respondents were invited to undergo further evaluation including endoscopic biopsy. Celiac disease was diagnosed on the basis of a positive serology, the presence of villous atrophy and/or response to gluten free diet.

Result: Among 12 573 contacted, 10 488 (83.4%) (50.6% male) agreed to participate. Based on screening, 5622 (53.6%) participants were screen positive. Of all those screen positive, 2167 (38.5%) agreed for serological testing; additionally 712 (14%) negatives were also tested. The overall sero-prevalence of celiac disease was 1.44% (95% confidence interval [CI] 1.22 1.69) and the overall prevalence of celiac disease was 1.04% (95% CI 0.85 1.25).

Conclusion: The prevalence of celiac disease in this north Indian community is 1 in 96. Celiac disease is more common than is recognized in India.

Introduction

Celiac disease is a chronic systemic autoimmune disorder induced by gluten proteins present in wheat, barley, and rye. Until the late 1970s, the suspicion of celiac disease was based mainly on clinical symptoms such as diarrhea, malabsorption and weight loss. The disease was considered to be rare; the prevalence was estimated to be as low as 0.03% worldwide.[1] Subsequently, the disease has been found more frequently in adults suffering from a variety of atypical symptoms and even in asymptomatic subjects.[1] With the realization of the diversity of manifestations of celiac disease and availability of highly sensitive and specific serological tests, anti-endomysial antibody and anti-tissue transglutaminase antibody assays, a certain increase in its occurrence was observed. Screening studies in different populations have shown that the prevalence of the disease is much higher than previously thought, 1% or more in both the United States and Europe.[2–5] The prevalence of detected cases of celiac disease is much lower, from 0.27% to 0.02%. This means that, for every patient with the diagnosis of celiac disease, 3–10 remain undetected. It thus became apparent that, without active serologic screening, the majority of celiac cases would remain undiagnosed.

There is a general perception that celiac disease is uncommon in India. As the origin of north Indians is Indo-European, it is likely that celiac disease would be more common in north India than previously thought. Sood *et al.*[6] from Ludhiana reported a rising number of celiac disease cases in their hospitalized patients over the last 10 years. In recent years, celiac disease is recognized much more frequently in India not only in children but also in adults.[7–14] In a recent report from Ludhiana, Sood *et al.*[15] reported a

prevalence of celiac disease to be 1 in 310 after a questionnaire based survey of 4347 school children (aged 3–17 years). There is a lack of population-based studies on the prevalence of celiac disease in both children and adults.

Therefore, we conducted a pilot study to find out the prevalence of this condition in the National Capital Region of Delhi, India. This study included population from rural as well as urban settings.

Methods

Study setting

The study was conducted in the urban and rural field practice areas of the Centre for Community Medicine, All India Institute of Medical Sciences (AIIMS) between October 2008 and December 2009. The urban area consisted of six blocks of resettlement colony of Ambedkar Nagar in south Delhi (Block 1,2,3,4,6,14) which is served by a mobile health van from AIIMS. The rural practice consisted of 28 villages in the Ballabgarh block of Faridabad district and is served by sub-centers, two primary health centers and a sub-district level hospital at Ballabgarh.

Sample size calculation

Sample size was estimated to be 9900 subjects based on an assumed prevalence of 1% and a relative precision of 20% (0.8% to 1.2%). Thus, if two individuals, that is one adult and one child, were to be taken in the study from each selected household, approximately 5500 households (HHs) were required assuming a 10% refusal rate. The sample size of 11 000 was divided as 3000 from urban and 8000 from rural areas reflecting the proportion in the country.

Sampling units

For the urban area, households were selected from all six blocks from the abovementioned area. For the rural area, using proportionate to population size sampling, a list of 12 villages was selected for survey. These included Macchgarh, Sotai, Shahpur Kalan, Jawa, Panehra Kalan, Fatehpur, Chandawali, Chhainsa, Dayalpur, Mauzpur, Atali and Dayalpur Khera.

Selection of households

The field investigators were trained to administer the pre-designed questionnaire and were instructed to administer the questionnaire to every alternate household. The field investigators worked in two teams of two each. One team covered the urban area and the other one the rural area. The teams were provided structured survey sheets, and using these they listed and enrolled households as they went along with their survey. Any refusals or locked households were also recorded in the sheet. After self-introduction the field investigators informed the households about the purpose of their visit. Written and informed consent was obtained from all the adult participants. In case of children, the consent was obtained from the parent or guardian at the time of the visit. The study was approved by the Ethics Committee of our institution.

Selection of individuals

It was decided apriori that from each selected household one adult (defined as individual aged 18 years to 64 years) shall be included in the study. This could either be a male or, a female member of the family. Additionally, if there was a child aged between five and 17 in the family, one child either a male or a female was to be selected.

To aid selection of the gender of the adult to be interviewed from a household, each team was provided a pre-randomized list. A similar list was provided for the children. For selecting one adult of the gender out of all adults of the same gender in a household, the names of all adult members of the selected gender in the household were listed. Then using a dice, one member was selected. The selected individual's consent was taken and an identification (ID) number was assigned. Children were selected in the same manner as the adult was selected. If there were no children in a particular household or if a child of the gender to be included (as per the pre-randomized list) was not available, then no children were selected from the said household.

The following criteria were used to screen suspected cases of celiac disease for further evaluation and an adult was considered screen positive if any of the following findings were present[14]:

1 History of chronic or recurrent diarrhea (i.e. an increase in the frequency and liquidity of stools above normal, for $\geq$ 2 weeks) with or without abdominal pain.
2 Pallor on examination.

Children included in the study were considered as screen positive for celiac disease if they had either of the above mentioned findings or they were:

1 Short statured (i.e. linear height below the 5th percentile for age in the absence of any other specific identifiable cause).
2 Or there was failure to thrive or, gain weight (i.e. a weight for age below the 5th percentile).

Testing strategy

As this was a pilot study, and the expected prevalence of the disease was low, it was decided to adopt a two stage process of screening, followed by serological testing. In order to validate the screening process, it was decided to include 10% of the screen negatives also for serological testing. They were tested for anti-tissue transglutaminase antibody (anti-tTG ab). Those who were anti-tTG ab positive underwent further evaluation including duodenal mucosal biopsies.

Questionnaire based classification

The participants were divided into screen positive (if positive by the screening criteria mentioned above) or screen negative. All of the screen positive participants and a randomly selected 10% subsample of screen negative participants were invited for blood test at blood collections camps. These camps were held in places in the vicinity of the surveyed areas, for example, in the same block in urban areas or in the same village in the rural areas. Appointment slips were distributed to each participant in respective village and block 2 days prior to the camp by the field investigators. During the camp the study was once again explained to the participants. Individuals were identified by specific six digit code IDs printed

on their appointment slips. The identity was rechecked and 4.5 mL of blood was drawn under standard conditions. The labeled tubes were transferred in an airtight box filled with cold gel bricks to maintain the box temperature at 4°C and transferred to the laboratory in a cold chain. The serum separating tubes were centrifuged the same day. Three aliquots of sera were stored in properly labeled 1.5 mL tubes at −80°C. Of these, two aliquots were used for enzyme linked immunosorbent assay (ELISA).

Screening test for celiac disease

The IgA-human anti-tissue transglutaminase (tTG) antibody testing was done using commercially available ELISA kits (The Binding Site Limited, Birmingham, UK). The ELISA was done in duplicate in all of the sera samples as per the manufacturer's instructions. Positive and negative controls were used. An anti-tTG titre of > 4 U/mL was considered as positive for celiac disease in the current study.

Further evaluation for celiac disease

Those subjects found to be positive by ELISA were contacted and were invited for further tests as per protocol including detailed clinical evaluation, hematological and biochemical tests, upper gastrointestinal endoscopy and duodenal biopsies. Endoscopic examination was done using a video-endoscope and four pieces of biopsies were taken from the second/third part of the duodenum. All of the biopsies were reviewed by an expert pathologist, blinded to the case histories. Histopathology was expressed according to the Marsh classification of 1992.[16] Wherever the biopsies were poorly oriented, step cuts were taken and biopsies were reviewed.

Diagnostic criteria of celiac disease and management

The criteria for the diagnosis of celiac disease were: (i) a positive anti-tTG ab and (ii) an intestinal biopsy showing villous abnormality. All respondents who were suspected to suffer from celiac disease based on screening symptoms, a positive anti-tTG ab positive and villous atrophy, were counseled about the disease, its natural course and available treatment. All of them were counseled by a nutrition specialist and advised to take a gluten free diet. In addition, they were also given hematinics for treatment of anemia, calcium supplement and multivitamin. A follow-up was also made at 3 months.

Quality control

During the study, supervisory visits were done and random checks were carried out regarding the screening of the subjects. Every 4–6 weeks, review meetings were conducted by study personnel and data were reviewed time to time.

Statistical analysis

All of the filled questionnaire sheets were entered into a computer using Epi-info Version 3.4.1 (CDC's database and statistics software for public health professionals). Double data entry was done for quality control. Entered data were analyzed to assess the characteristics of the study population, namely, age and gender distribution and the screening criteria. Means, proportions and 95% confidence intervals were calculated using STATA 9.1.

The screen positive and screen negative categories and the respondents who attended blood collection camps and those who did not attend were compared statistically using χ^2 test or ANOVA test. While comparing population prevalence, the final prevalence rates were adjusted to the non-response rate at different levels.

Table 1 Screening of population

	No.	Screen positives	Screen negatives
Total population screened	10 488	5622 (53.6%)	4866 (46.4%)
Adult	6 845	3261 (47.6%)	3584 (52.3%)
Male	3 415	932 (27.2%)	2483 (72.7%)
Female	3 430	2329 (67.9%)	1101 (32.0%)
Children	3 643	2361 (64.8%)	1282 (35.1%)
Male	1 890	1199 (63.4%)	691 (36.5%)
Female	1 753	1162 (66.2%)	591 (33.7%)

Results

Screening

A total of 12 573 households were visited and of them 10 488 (83.4%) agreed to participate (rural community 7484 [71.3%] and urban community 3004 [28.6%]). Based on the study criteria, 5622 (53.6%) were found to be screen positive. All of the screen positive respondents and 10% of the screen negatives were invited for blood testing, that is, testing for anti-tTG antibody. However, 2167 (38.5%) of the screen positive group and 712 (14.6%) of screen negatives attended camps held for blood collection. These findings are summarized in Table 1. The flow chart in Figure 1 provides an overview of the study.

From Table 1, it is clear that among adults a higher proportion of females was found to be screen positive for celiac disease as compared with males. This gender difference was not observed among children.

To rule out the presence of any selection bias, the screen positive respondents who subjected themselves to blood test (anti-tTG ab) and those who did not undergo serological testing were compared statistically. The findings are depicted in Table 2. From the table it is evident that there was no difference in the age and clinical symptoms in the two groups, except that the people who attended blood collection camps were more likely to be females and less likely to have pallor. Lesser male participation can be attributed to their being not available due to work.

Estimation of prevalence of celiac disease in the study subjects

A total of 2879 blood samples analyzed using anti-tTG ab, of these 2167 were carried out among screen positives and 712 in screen negatives. Of these, 50 were anti-tTG Ab positive, 45 of these were

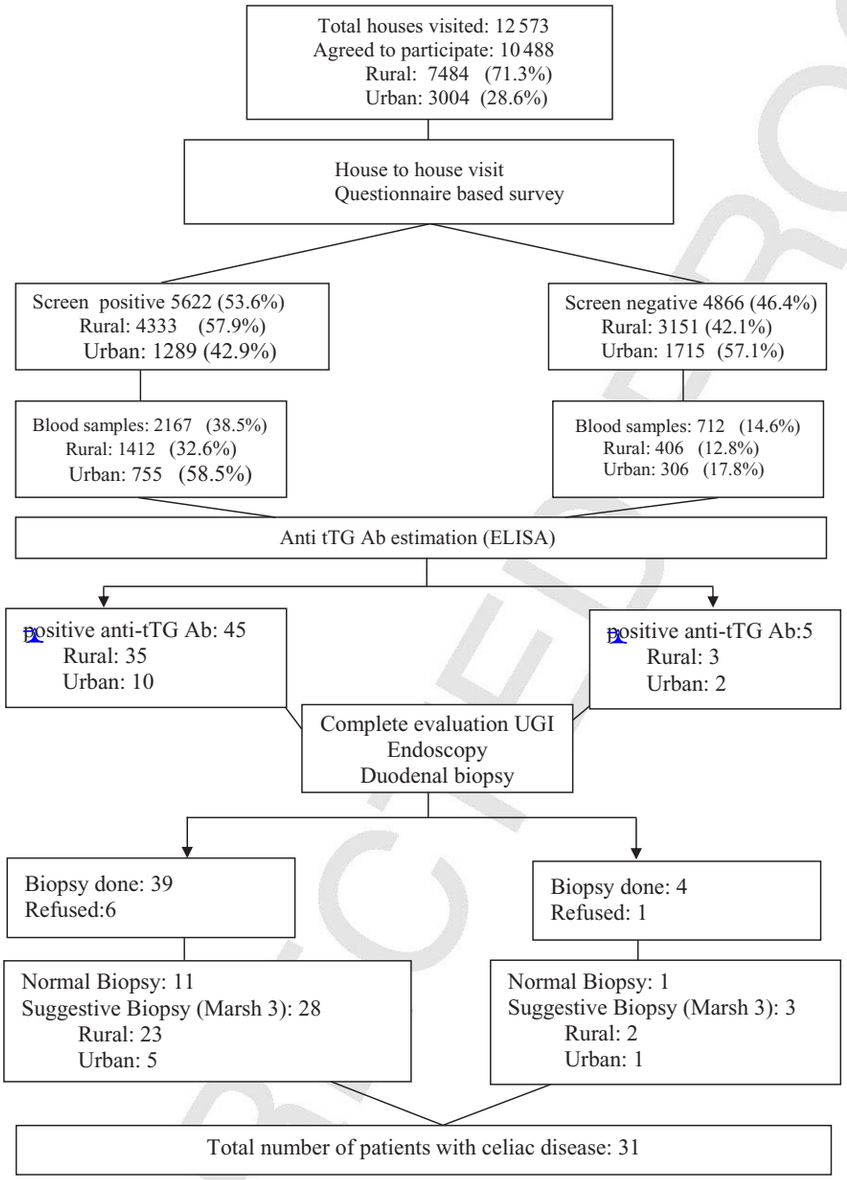

Figure 1 Flow diagram: The conduct of the study and results.

among the screen positives and five among the screen negatives. These study subjects underwent further investigations including endoscopy and biopsy.

Two of these 50 patients were already known cases of celiac disease. Of all others with a positive anti-tTG-ab, seven denied further evaluation including endoscopic examination and duodenal mucosal biopsies. In 12 anti-tTG ab positive subjects, the duodenal biopsy was normal. Finally 31 patients were diagnosed to have celiac disease.

To estimate the prevalence at the community level, the following steps were undertaken:

1 As screen negative subjects also tested positive for anti-tTG Ab, this was corrected for by applying the rate of positive serology among all screen negative responders (0.70%) to all of the screen negative individuals.
2 As there was no difference in clinical characteristics between those who had serological tests compared with those who did not; the rate of positive anti-tTG ab among those who underwent anti-tTG testing (2.08%), was applied to those who did not undergo anti-tTG testing.

The total subjects estimated to be positive after applying this correction among the screen positive and the screen negative subjects was totaled to estimate the prevalence rates. Thus, the seroprevalance of celiac disease (anti-tTG ab) was estimated to be 1.44% (95% confidence interval [CI] 1.17 1.63). Applying the same principles for calculating the prevalence of biopsy proven

Table 2 Characteristics of subjects and their symptoms in those who underwent serological test and those who did not in both screen positive and screen negative groups

Demographic features	Screen positive		*P*-value	Screen negative		*P*-value
	5622 (53.6%)			4866 (46.4%)		
	Subjected	Not subjected		Subjected	Not subjected	
Mean age (years) (Adults)	36.1 ± 10.6	35.4 ± 10.4	0.074	33.9 ± 11.1	32.4 ± 10.5	0.008
Mean age (years) (Children)	11 ± 3.6	10.8 ± 3.9	0.242	10.8 ± 3.6	10.9 ± 4	0.668
Gender (adults) Proportion males	22.5%	32.3%	< 0.001	59.3%	68.9%	< 0.001
Gender (children) Proportion males	51.5%	50.3%	0.297	56.9%	51.6%	0.150
Chronic diarrhea	18.2	19.5	0.119	0	0	n/a
Pallor	66.1	69.9	0.003	0	0	n/a
Short stature (only in children)	71.1	73.1	0.306	0	0	n/a
Failure to thrive (only in children)	87.4	86.8	0.678	0	0	n/a

Table 3 Prevalence of celiac disease in the study population

Subjects	Total no. subjects	No of subjects tested for tTG	Positive tTG Actual [Corrected]	Sero-prevalence (95% CI)	Suggestive biopsy Actual [Corrected]	Celiac disease prevalence % (95% CI)
Screen positive	5 622	2167	45 [117]	2.08% (1.72 2.49)	28 [84]	[1.49%] (1.19 1.85)
Screen negative	4 866	712	5 [34]	0.70% (0.48 0.97)	3 [25]	[0.51%] (0.33 0.76)
Overall	10 488	2879	50 [151]	1.44% (1.22 1.69)	31 [109]	[1.04%] (0.85 1.25)

Table 4 Prevalence of celiac disease in different population sub groups

Subgroup	Corrected sero-prevalence (95% CI)	Corrected prevalence of celiac disease (95% CI)
Adults ($n = 6845$)	1.10% (0.86 1.37)	0.85% (0.64 1.09)
Children ($n = 3643$)	2.06% (1.62 2.57)	1.41% (1.04 1.84)
Males ($n = 5305$)	1.28% (1.00 1.62)	0.91% (0.67 1.20)
Females ($n = 5183$)	1.60% (1.28 1.98)	1.20% (0.92 1.53)

CI, confidence interval.

celiac disease was found to be 1.04% (95% CI 0.85 1.25). These findings are summarized in Table 3.

Seroprevalence and prevalence of celiac disease in children and adults and males and females are shown in Table 4.

Among the 31 patients with celiac disease, nine (29%) had symptoms of chronic or persistent diarrhea, and 21 (67.7%) had pallor. Among 18 children with celiac disease, 11 (61.1%) of them were of short stature and 15 (83.3%) showed failure to thrive.

Follow up

All patients were advised to take a gluten free diet. While 21 showed response to treatment; four were non-compliant to gluten free diet and six refused to start gluten free diet.

Discussion

In recent times, there has been not only an increase in the number of patients with celiac disease but it has been reported from many centers in India.[1] In the first community based study including both children and adults from an Asian region, we observed the prevalence of celiac disease in the northern part of India to be 1.04% (1 in 96) and the prevalence of positive serological test (anti-tTG ab) to be 1.44% (1 in 69). In another study, Sood *et al.*[15] reported a prevalence of celiac disease to be 1 in 310 based on a questionnaire-based survey including 4347 school children (aged 3–17 years). Lal *et al.*[17] in another study from Chandigarh (northern part of India) reported a seroprevalence of celiac disease to be 1:120 in healthy school children. Based on these three community-based studies, 5–8 million people are expected to have celiac disease in India. Of such a large pool of patients, only a few thousand patients have been diagnosed as having celiac disease and a large number of subjects are still undiagnosed.

The results of the present study along with that reported by ~~by~~ Sood *et al.*[6] suggest that celiac disease is a much greater problem in India than has been thought previously. The prevalence of celiac disease in an Indian community is nearly the same as that reported from the European nations and United States.

Celiac disease is not a new disease in this part of the continent; it is known to have occurred in India for a long time and was first described in the 1960s by Walia *et al.*[18] in children and Misra *et al.*[19] in adults. Subsequently, Nelson *et al.*[20] reported a series of 17 immigrant Asian children with celiac disease from Birmingham. Thereafter, there was a long silence about the occurrence of celiac disease in India.

Most of the subsequent reports on celiac disease have appeared from the northern part of India (Punjab, Haryana, Delhi, Rajasthan, Uttar Pradesh) where wheat is the staple cereal in the diet.[6,11–15,21–27] Celiac disease has also been reported, although in only a few patients, from Maharashtra (Western India), Chennai and Vellore (southern part of India).[28] The reason of such a phenomenon is not known. Is it the dietary factor (as rice is the staple food in the southern part of India) or people of this region are genetically

protected? Although rice is the staple cereal in the southern part of India, there ~~however~~ has been a change in the dietary behavior and wheat products are now included, albeit occasionally, in their diet. There is an urgent need for epidemiological study (using serological tests for screening) to estimate prevalence of celiac disease in different regions of India. If there is a real difference in the prevalence of celiac disease in northern and southern parts of India, India might prove to be a model to understand the genetics of celiac disease and ethnic variations in celiac disease.

Celiac disease has been recognized by pediatricians and there has been a notion and belief that celiac disease is a disease of children and does not occur in adults, ignoring the fact that all these children will grow into adults later. This is now well appreciated that almost half of patients with celiac disease do not present with classical presentation such as chronic diarrhea. Instead the primary manifestations in them could be short stature, anemia, infertility, and osteoporosis and they may first report to physicians other than gastroenterologists such as endocrinologists, hematologists, gynecologists or orthopedicians, respectively. Because of the lack of awareness in these specialties, a diagnosis of celiac disease is generally not considered.

If celiac disease is as common in India as shown by the present study and another study by Sood *et al*.[15] then what are the reasons for under-diagnosis of this disease? Foremost among the possible explanations is the belief of many physicians that celiac disease is rare/uncommon in this part of the world and therefore the eligible patients are not investigated for celiac disease. Presentations with non-gastrointestinal manifestations such as short stature, anemia, osteopenia or infertility may be another reason for missing of the diagnosis. Finally, failure by pathologists to recognize early features of celiac disease (Marsh stages 1, 2, and 3a) is also an important issue not only in India but in other regions also.

The diagnostic criteria for celiac disease requires small-intestinal mucosal villous atrophy with crypt hyperplasia (Marsh III). However, mucosal damage develops gradually and patients may develop clinical symptoms even before classical histological changes have appeared. Two recent studies by Kurppa *et al*.[29,30] all have elegantly demonstrated that even those with a positive serology and no villous atrophy do respond to a gluten free diet. In a subset of patients having Marsh I–II histology and positive serology, Kurppa *et al*.[30] in a randomized controlled trial demonstrated alleviation of symptoms, decrease in antibody titers and improvement in histology in those who were randomized to receive gluten free diet while there was deterioration in the small intestinal lesions in those who were continued on a gluten diet. In another study, the same author showed similar observations in 17 anti-endomysial antibody positive children with either completely normal histology (Marsh 0) or at most Marsh I lesions. These two studies are quite intriguing and may lead to a change in the diagnostic criteria of celiac disease.

We also observed that many of these patients were symptomatic for long and despite having symptoms they did not seek medical care. In fact, 10 patients with both a positive serology and having villous atrophy either refused initiation of gluten free or had a poor compliance to treatment despite repeated home visits by the investigating team. In the time to come, this is likely to be a challenge for the physicians dealing with celiac disease in India. At present, there is a lack of reliable commercially available gluten free food products in India.

There are a few limitations of this study. While a mass serological screening is a preferable and recommended strategy for the estimation of prevalence of a disease, we used a three step approach in this study based on screening. Even amongst those who were screen positive, the serological test could be done in only 38.5% of subjects. Five of 712 screen negative subjects in the community were serology positive; however, biopsy was abnormal in three of them. This was adjusted for while calculating the prevalence of celiac disease in the study population. Therefore, many others with no symptoms might have been missed, as serological test was not done in all screen negative subjects.

Conclusions

The overall prevalence of celiac disease in North India is 1.04% (1 in 96). Such a relatively high prevalence of celiac disease challenges the age old belief that celiac disease is uncommon in India. There is a requirement to enhance the awareness of celiac disease not only in the community but also among physicians. It is now a challenge and opportunity to bring the celiac disease to the surface in India.

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