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Seroprevalence vs Biopsy Prevalence of Celiac Disease: A Bird's Eye View

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Abstract Celiac disease (CD) is an autoimmune disorder precipitated generally in genetically susceptible individuals by the ingestion of gluten and is becoming a major communal health problem throughout the globe. Initially the disease was reported in few of the countries specifically in predominant Caucasian populations, but now a day it is being reported from almost all parts of the world. Simplification of the diagnostic criteria and widespread use of serologic tests have made it possible to estimate the prevalence of CD in the general population. But the exact global prevalence of the celiac disease is quite ambiguous due to the fact that when the disease is diagnosed with tTG test it is generally not confirmed with the biopsy examinations whereas, diagnosis should be based on the combination of both as per current guidelines on diagnosis of CD. The seropositive based (anti-tissue transglutaminase and/or anti-endomysial antibodies) data shows a high global prevalence of 1.4% whereas biopsy-confirmation based data shows a global prevalence of only 0.7%. Although prevalence of celiac disease varies with respect to sex, age, and location etc. but its accurate prevalence is not being reported due to various reasons. At the same time, a classified data of prevalence of the celiac disease based on multiple factors does not exist. This manuscript intends to highlight various underlying reasons responsible for generating vague prevalence data worldwide along with an awareness note regarding practical implications of diagnostic modalities.

Keywords: *celiac disease, biopsy, tTG, first degree of relevant*

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1. Introduction

Celiac disease (CD) is an autoimmune disorder generally precipitated in genetically predisposed people on exposure to gluten a protein present in wheat, rye, barley and oats [1]. The exposure of gluten leads to damage of their intestinal mucosa leading to poor absorption as well as distribution of food and finally resulting in malnutrition. In fact body of people with celiac disease upon ingestion of gluten show an immune response which attacks the small intestine. These attacks cause damage to the villi that are small finger like projections lining the small intestine responsible to promote nutrient absorption. When the villi get damaged, nutrients remain unabsorbed in the body. This interplay between gut microbiota and the mucosal immune system is supposed to play a major contribution in CD [2,3].

It has been observed that celiac disease is considered to be genetic disease as it runs within families depending upon their HLA typing. In a family, if a person is suffering from celiac disease, first-degree relative such as parent, children, or sibling, have a possibility of developing the disease and the probability of the same is 1 in 10. As CD is an autoimmune disorder so, genetic factors play an important role in the development of the disease. The major genetic risk factor involved in CD is found to be HLA-DQ genes. Around 90% of the affected individuals carry the HLA-DQ2 haplotype, 5% carry the DQ8 haplotype, and the other 5% carry at least one of the two DQ2 alleles [4,5].

Although genetic predisposition plays an important role in the development of CD but as per the previous reports it has been revealed that the HLA gene itself is not sufficient for the development of disease [6]. As per the data available, it has been observed that around 30% of the general population carries the HLA-DQ2/8 CD susceptibility genes, however; only 2-5% among them will develop CD, suggesting that additional environmental factors are also contributing to disease development [7].

Now days, CD is becoming a common health problem issue as the disease is distributed worldwide throughout the globe, with considerable variation in prevalence even amongst geographically proximate populations. The prevalence of CD is about 1% to 3% of the population, in most of the areas of the world [8] and its incidence has been reported to increase consistently during the past

several decades [9]. The disease can grow at any age in life, from childhood to late adulthood but in reality 83% of the population having celiac disease is not being diagnosed because of many varying symptoms that further vary from person to person. For example, a person may have constipation; the other may have diarrhoea while the third may not have any difficulty with stool pattern [10]. Celiac disease is highly unpredictable and individual-specific. Moreover the symptoms of celiac disease are typical, atypical or associated with some other conditions as shown in Figure 1.

Most of the CD individuals are predominantly symptomatic, showing both gastrointestinal and extra-intestinal manifestations whereas in asymptomatic patients the diagnosis is often delayed and due to this, the small-bowel mucosal damage may be severe till celiac disease is suspected.

Although prevalence of celiac disease varies with respect to sex, age, and location etc. but its accurate prevalence is not being reported due to various reasons. Even the published data by a number of scientists for different countries have overlooked various factors attributing to increased prevalence of the disease. At the same time, a classified data of prevalence of the celiac disease based on multiple factors does not exist. This manuscript intends to highlight various underlying reasons responsible for generating vague prevalence data worldwide along with an awareness note regarding practical implications of diagnostic modalities. The present manuscript has been compiled to review the prevalence data of Celiac. The article will be further helpful to reflect the practical implications of diagnostic modalities which are being used for the diagnosis of the disease. In addition, article will help to unfold other dimensions as well as clinical parameters, of the disease in India and abroad.

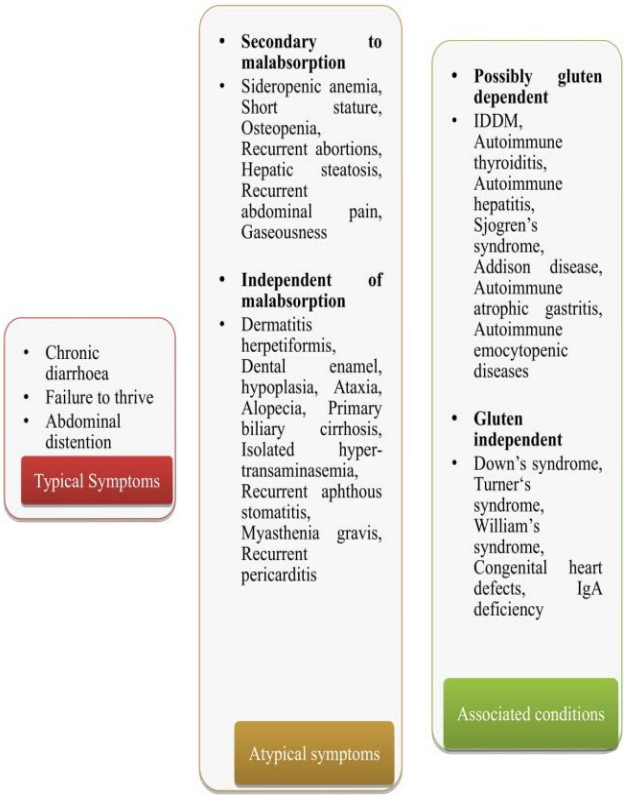

Figure 1. Symptoms of celiac disease

2. Prevalence of Celiac Disease Worldwide

Celiac disease is becoming a major communal health problem throughout the globe. Initially the disease was reported in few of the countries specifically in predominant Caucasian populations, but now days it is being reported from almost all parts of the world. Simplification of the diagnostic criteria and widespread use of serologic tests have made it possible to estimate the prevalence of CD in the general population [6,11]. But the exact global prevalence of the celiac disease is quite ambiguous due to the fact that when the disease is diagnosed with tTG test it is generally not confirmed with the biopsy examinations whereas, diagnosis should be based on the combination of both as per current guidelines on diagnosis of CD [6]. The prevalence of the disease is being calculated in both ways i.e. with tTG only and after biopsy confirmation also. As per the literature review it has been observed that pooled global seroprevalence and biopsy-confirmed prevalence of CD was 1.4% and 0.7%, respectively [12,13,14]. From the previous reports, it has been observed that, the prevalence of CD is about 1% to 3% of the population, worldwide. Moreover, its incidence has been reported to increase consistently during the past several decades [15]. The prevalence of CD has been depicted in Figure 2.

Figure 2. Representation of %age prevalence of Celiac disease throughout the globe [16]

Historically CD was supposed to be prevalent in the areas where grains containing gluten are used as staple diet but with time it has been observed that incidence of CD is increasing even in CD free areas due to significant changes in diet and other environmental factors [17]. In Western countries several recent studies evaluated the overall prevalence of CD in the general population and according to the published reports; the mean frequency of CD was around 1% in Europe and United states [18,19]. At the same time, the prevalence of the same was found to be higher in the countries like Finland and Sweden i.e. 2% and 3% respectively. In the countries like Germany, the prevalence recorded is 0.2% only despite of the fact that this country shares almost similar factors such as level of gluten intake and frequency of HLA-DQ2 and -DQ8), [18,20]. In comparison to previous years, the overall prevalence of CD is increasing in Western countries as an

increase of 6.4 fold and 5 fold has been found in countries like Scotland and United states respectively [21,22]. The major reason contributing to the increased incidence of CD includes malnutrition, frequency of HLA- DQ2 and DQ8 genes, changes in quality and quantity of grains having gluten, feeding patterns in neonates, changes in gastrointestinal microbiota due to increased spectrum of intestinal infectious diseases and other environmental factors.

As per a systematic review and meta-analysis conducted by Singh and his coworkers in 2017, it has been observed that seroprevalence was same in various countries whereas biopsy-confirmed celiac disease prevalence was found to be slightly lesser in South America, the Middle East, Turkey, and sub-Saharan African areas [16]. In addition, it also has been observed that population-based studies from the far-East, including China, Japan, and Southeast Asia except Malaysia and Vietnam are lacking [23,24,25]. The geographical prevalenc9e of celiac disease based on serological tests in contrast to biopsy testing of various continents is shown in Figure 3.

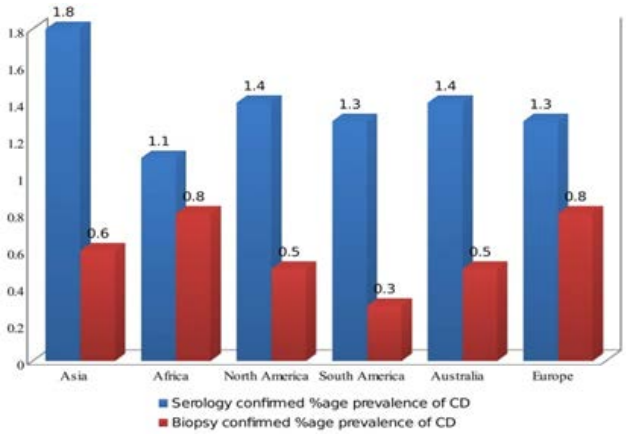

Figure 3. Prevalence of celiac disease based on serological tests in contrast to biopsy testing in various continents [16]

In addition, it is pertinent to mention that prevalence data is vague because there are varying symptoms of the disease and hence many of the patients remain undiagnosed due to asymptomatic development of the disease. Most of the biopsy confirmed prevalence of CD was found in Africa and Europe as shown in Figure 3 because the data of seroprevalence and biopsy testing is quite similar.

According to a recent analysis, gender and age based prevalence of Celiac Disease was found to be slightly more prevalent in women than in men and slightly more in children in comparison to adults. As per the clinical practice data, it has also been demonstrated that two third of the diagnosed patients are females and hence are supposed to be more affected by the celiac disease [16]. Similarly it is clearly mentioned in the reports that children of age 0-14 years are more prone to the disease in comparison to the adults. The geographical representation on the basis of gender and age is shown in Table 1.

The children are slightly more affected by this disease due to various reasons such as early exposure to gliadin protein to child, introduction of gluten in the diet at early childhood, genetic background as well as wrong eating habits [26-31].

Table 1. Gender and Age-Wise Prevalence of Celiac Disease Along With Causative Factors [16,28,32,33]

Gender /age group	Total Population screened for CD (By biopsy)	Confirmed CD	%age prevalence	Reason for CD
Male	33,149	156	0.4	Exposed to other autoimmune disorders.
Female	27,371	213	0.6	HLA genes
Children	65,957	891	0.9	• Early exposure to gliadin protein • Dose of gluten • Introduction of gluten at an early age • Genetic factors
Adult	40,076	276	0.5	Diet, HLA genes

3. Prevalence of CD in India

The knowledge of the epidemiology of CD in the Asia Pacific region is still limited and mostly confined to India, where CD is being more frequently recognized, both in children and adults [34]. The celiac disease was reported in India in the late 1960's especially in children and remained silent till 1988 [35,36,37,38] due to lack of awareness about the disease, lack of appropriate diagnostic tests and even due to lack of biopsy based confirmatory tests [39]. As per current scenario in India, awareness as well as progression of the disease is progressively increasing. However, as efficiently described by an Indian task force, CD in India is considered to be a disease which is submerged in an ocean of malnutrition [40]. The frequency of CD in India seems to be higher in the northern part of the country, so called ''celiac belt,'' because most of the cases are reported from regions like Punjab, Haryana, Delhi, Uttar Pradesh etc. [41-45] The major reason of prevalence of celiac disease in northern area is partially explained by the wheat-rice shift from the North to the South [45]. However the cases are being reported from other regions also but the reasons of the prevalence in other areas is lesser due to the fact that wheat is not their staple diet and in most of the patients it has been observed that either they are migrated from other areas or they have included both wheat and rice in their diet or even due to genetic predisposition.

Previous studies reported a high prevalence of 198 out of a sample of 4347 (means 1 in 310) in the regions such as Punjab. In the general population the prevalence of the disease varies between 0.3- 1%. As per another study, the prevalence of Adult Celiac Disease in India has been demonstrated by Ramakrishna et al, 2015, India has been divided into three zones named North India, South India and North Eastern India and out of the total 23,331 people tested for CD by IgA tTG test, 158 were found of having positive test result. According to the study, the overall prevalence was found to be 0.6%. In addition, it has been observed that prevalence of CD was found highest in the population of north India where wheat is the staple food and least in South India where rice is the major staple food. The least prevalence in the South India demonstrates the relation of celiac disease with ingestion of wheat which is

the major cause of CD in India [46]. The % age prevalence of CD in various regions is shown in Table 2.

Table 2. Prevalence of CD in India based on different Zones [46,47]

Zone	Total Population screened for CD (By IgA- tTG)	Confirmed CD	%age prevalence
North India	6209	76	1.2
North Eastern India	8149	70	0.9
South India	8973	12	0.1

As shown in above data, the Northern regions are more prone to the disease and hence it has been observed that prevalence of CD in Punjab, Delhi, Rajasthan, Uttar Pradesh, Bihar and Madhya Pradesh are predominantly higher on epidemiological basis in these states [46,47]. The studies in Delhi and Uttar Pradesh are following similar trends as followed in the European countries. Apart differences in region based prevalence it has been observed that the prevalence of CD was found to be more in urban area than in rural area i.e. 0.8% and 0.6% respectively as shown in Table 3.

Table 3. Distribution of Prevalence of CD in rural and urban India

Area	Total Population screened for CD (By IgA- tTG)	Total no. of subjects with confirmed CD	%age prevalence
Urban	8,181	62	0.8
Rural	15,150	96	0.6

Moreover, it also has been observed that first degree relatives of the diseased person are more prone to the disease. Singh and his co-workers in 2016 have observed that the prevalence of the celiac disease in first degree relatives is found to be 8.9% on the basis of antibody based assay and it is found to be 17.3% on the basis of the biopsy testing. According to their study it has been observed that the study is approximately 10 times more prevalent in the first degree relatives in contrast to the general population. The major possible reason of such a higher prevalence is genetic origin, similar staple diets etc. In addition, it also has been observed that the prevalence is higher amongst the siblings in comparison to the parents. In one of the similar study conducted by Grover and his co-workers, 169 first-degree relatives consisting 66 parents, 71 siblings and 32 children were screened. Amongst them the prevalence of first degree relative was found to be 8.2% i.e. (14/169) whereas the prevalence of celiac disease in siblings is found to be (15.6%) in comparison to parents (3.5%) and the offspring (3%) of the diseased person. Thus in future, determination of the familial prevalence is the need of the hour in view of genetically diverse population of India [46,47].

According to the previous studies, it has been reported that the prevalence of the disease is more in female in comparison to males i.e. 0.8% and 0.5% respectively as shown in Table 4.

Table 4. Prevalence of CD in India based on Gender [46]

Gender	Total Population screened for CD (By IgA- tTG)	Total no. of subjects with confirmed CD	%age prevalence
Male	10,776	58	0.5
Female	12,555	100	0.8

Apart gender based differences, in the initial years it was observed that difference of prevalence of celiac disease do exist on the basis of age group. In the early years it was supposed that the disease is found to be more in children in contrast to adults in India but as a matter of fact the disease can develop at any time from infancy to old age. Initially the children were diagnosed for the celiac disease but now-a-days the trends are changed and celiac disease is diagnosed in the adults too in India and even throughout the globe.

4. Prevalence of Celiac Disease in First Degree Relatives

Celiac Disease is a genetic disease and hence the both first degree relatives as well as second degree relatives are supposed to be on high risk. The higher genetic susceptibility of celiac disease has been observed in the first degree relatives of the patients due to a strong genetic repertoire of HLA gene specifically its subtype HLA-DQ 2 and HLA-DQ8. Moreover, these First Degree Relatives probably share similar environmental triggers for the development of the disease [48]. Although aggregation of the genes in the families is common but the prevalence rate of 18%, 75% and 40 % been observed in sibling pairs, monozygotic twins and identical twins respectively [49]. According to various reports it has been reported that prevalence of the disease in first degree relatives varies from 5-38% whereas studies conducted in Asia represented the prevalence of the disease in the range 8.2% to 22% [50]. The spectrum of the disease is variable due to the fact that most of the patients remain asymptomatic or develop some mild symptoms that are confused with some other diseases. Actually the rate of the prevalence in the first degree relatives entirely depends upon the relationship index of the relative to the patient. In addition to it, the major reasons of the variation in the prevalence are as follows:

- Lack of awareness regarding genetics of celiac disease and it runs within families [51].
- First-degree relatives of families with single and multiple CD cases do not undergo the diagnosis due to the fact that either they are asymptomatic or have mild symptoms.
- Lack of histological confirmation of the diagnosis of CD in the first and second degree relatives due to mild or no symptoms.
- Lack of HLA typing as a reliable diagnostic tool as well as cost of the HLA typing [52].

The prevalence of the disease in first and second degree relatives reported in various studies has been compiled and an overall prevalence has been calculated as shown in Table 5.

Till date first degree relatives are not being diagnosed but screening of first degree relatives is desirable as early as possible. In addition, it is pertinent to mention that current serological test may not rule out the development of celiac patients in first/second degree relatives. Hence the use of HLA typing in the first/second degree relatives is highly recommendable through genetic studies such as HLA gene typing and in case of asymptomatic carriers, the tests should be repeated at appropriate intervals.

Table 5. Representation of Prevalence of the Disease in First and Second Degree Relatives

Population enrolled in study	Observed Prevalence	%age Prevalence	Major Outcomes	Reference
202	35	17.32	Prevalence of CD among FDR was found to be 9 fold higher than the general population	[53]
122	13	10.65	All the serology and biopsy tests were performed for the detection of CD. The seronegative patients were followed up further. Later on few more cases of CD was observed. This reviled that Reticulin-antibody positivity is an indicator of both silent and latent coeliac disease	[54]
4508	205	4.54	Most of the family members diagnosed with CD were asymptomatic.	[55]
188	9	4.8	The most important finding was that a negative result does not exclude the possible future appearance of CD in a relative of a CD patient.	[56]
484	46	9.50	-	[57]
441	40	9.07	HLA typing followed by serological test and Biopsy is essential for FDR in order to detect CD at early stage.	[58]
312	63	20.1	High-prevalence of CD was observed between CD Family members, and most of them were olygo- or asymptomatic.	[59]
434	58	13.36	HLA haplotypes are the major reason for CD. 87.4% FDRs had HLA-DQ2 or -DQ8 haplotype	[60]
91	9	9.89	HLA typing gives a possible estimation of CD in FDR and so it must be included as a tool for diagnosis in FDR of CD patients.	[61]
450	32	7.11	Earlier only 19 patients were diagnosed with celiac disease. Further follow-up for 10 years demonstrated increased evidence. 13 more relatives were further diagnosed with celiac disease.	[62]

5. Prevalence of Celiac Disease in Patients with other Autoimmune Disorders

Coexistence of two or more autoimmune diseases together is quite common but the prevalence of autoimmune diseases is increased in patients with celiac disease. Although the burden of co-existence of the disease is not same amongst all the patients yet multiple reports are evidencing an association between CD and various autoimmune diseases [63]. The prevalence of co-existence of celiac disease in the presence of other autoimmune diseases such as type 1 diabetes mellitus or thyroiditis is found to be 5% to 10%. On the contrary, the increased prevalence of other disease has been observed in patients with CD. According to another report it has been reported that 25% patients who already have developed any autoimmune disease are at risk of developing other autoimmune disease [64].

As per the current reports, it has been reported that factors associated with an increased risk of autoimmune disease are as follows:

5.1. Genetics Background

As per the current reports, it has been reported that the major predisposing factor for this association is the genetic background of the disease. Moreover it has been observed that pro-inflammatory cytokines are affecting the other auto-antigens followed by initiation of a new autoimmune attack [65].

5.2. Gene Linkage

It has been reported that the patients having family history of autoimmune diseases may have linkage between the genes associated with development of Celiac disease and the genes responsible for the other autoimmune disorders. Due to linkage amongst these diseases, the disease is co-expressed with other autoimmune disorders [60].

5.3. Time Period of Gluten Exposure

According to a study, it has been reported that risk of the autoimmune disorders was low in the late diagnosed patients whereas on the other hand it also has been reported that the risk of autoimmune diseases tend to decrease with prolonged gluten exposure [66].

5.4. Intestinal Injury

It might be possible that some of the auto immune diseases are responsible for intestinal damage due to some other reasons but that intestinal damage may be followed by villous atrophy or development of celiac disease. A person with any of autoimmune disorder is at high risk of developing CD early or late in their life. CD is found to be highly prevalent in various autoimmune disorders as shown in Table 6.

Table 6. Representation of Co-Existence of CD in The Presence of Other Autoimmune Disease

Autoimmune disease	Total Population/ Observed population of CD	% Prevalence of co-existence with CD	Outcomes
Autoimmune thyroid	6024/181	3.1	1 in 62 patients with Autoimmune thyroid disease suffer from CD and are generally asymptomatic [67]
Autoimmune Diabetes	52721/1835	3.5	CD is more frequent in patients with autoimmune diabetes mellitus and early screening for CD is recommended [68]
Inflammatory Bowel Disease	336/30	8.92	Serum tTG is found to be positive in many cases of IBD and prevalence of CD should be confirmed with biopsy [69]
Psoriasis	51/3	5.88	CD also has co-existence with Psoriasis. Damage to the intestinal membrane may be linked to the pathogenesis of skin lesions [70]
Autoimmune Hepatitis	64/3	4.8	Autoimmune hepatitis in co-existence with CD is found to be high. Due to asymptomatic CD patients accurate diagnosis is recommended in Autoimmune hepatitis patients [71]
Multiple Sclerosis	72/8	11.1	Higher prevalence of CD was observed in patients with multiple sclerosis without symptoms early screening for CD is recommended [72]

6. Critical Parameters Responsible for Vague Prevalence Data

The progression of the celiac disease has increased with the passage of time and as per recent reports the prevalence has reached 1-3% throughout the globe. The major reason of improved prevalence is increase in awareness about the disease as well as increased use of diagnostic techniques. It has been observed that prevalence data generated from serological tests and the other confirmatory tests is varying throughout the globe due to certain specified reasons. Although screening of the celiac disease (when and how) is a common and hot topic in almost all the countries but it is widely observed that the disease is still under-diagnosed.

6.1. Asymptomatic Patients

The prevalence data is being compiled by various scientists throughout the world but it seems to be vague because most of the cases rather majority of the cases remain undiagnosed due to lack of annotated symptoms or due to development of some uncommon symptoms. A very small chunk of the patients are being diagnosed for the disease due to availability of some specific and significant symptoms. The major reason of the same is that typical symptomatic patients are very less in number. Instead of symptomatic patients several mild or non gastrointestinal symptoms are currently more common rather majority of the patients are asymptomatic amongst newly diagnosed cases [73].

6.2. Lack of Standardized Tests

Another major reason of the under diagnosis of the disease is that in majority of the patients diagnosis relied only on highly specific serological tests. Currently serological testing using anti tTG antibody is quite famous test for diagnosis of the disease. It is helpful to confirm a great number of borderline cases in patients with mild intestinal lesions. It is likely that serology could identify celiac disease in its early stages, before the appearance of a severe intestinal damage. Serologic tests are generated in research setting and it is possible that the tests may perform less well in the clinical setting. On the other hand lack of test standardization of serological testing between commercial laboratories and hence variations in cut-off levels may affect the diagnosis of the disease and hence the disease is not diagnosed accurately [74].

6.3. Utility of Combination of Serological and Histological Test

Although duodenal biopsy is considered as a confirmatory test but most of the patients who are found to be positive in the serological tests did not undergo the biopsy confirmation which is an invasive technique and needs much more expertise to handle. Even in the absence of the confirmatory test, the patients undergo the treatment and are included under diseased category resulting in generation of vague prevalence data specifically in India. In addition it is pertinent to mention that the disease should be confirmed by both serological as well as histological test. Moreover false positive reporting in serological tests due to other food allergies or other intestinal infections is also an important reason of vague prevalence data of the disease and hence should be confirmed with gold standards [75].

6.4. Lack of Non-invasive Confirmatory Test

Small intestine biopsy/histopathology is an important element of the diagnosis and considered to be the gold standard for diagnosis due to histological changes (most relevant feature of the disease). Biopsy is an invasive procedure requiring lot of expertise. It has been observed that, careful and vigilant assessment of intestine during biopsy allows the accurate selection of celiac disease patients henceforth, at least four biopsy samples should be taken and intestine needs to be punctured many times. Despite of multiple punctures, physicians are unable to detect patchy villous atrophy or milder enteropathy leading to inaccurate prevalence data [73].

6.5. Co-existence of Other Diseases

Co-existence of one or more than one autoimmune diseases with similar type of symptoms is being reported. Celiac disease is an immune-mediated disorder clinically characterized by multiple symptoms and complications. The co morbidity between celiac disease and other autoimmune disorders has been clearly established. Sometimes patients have either no symptoms or confusing symptoms whereas on the other hand sometimes under the umbrella of one autoimmune disease celiac disease also develops with or without symptoms. In such cases, disease is not accurately diagnosed and hence prevalence data becomes unclear and inaccurate [74,75].

6.6. Inconclusive Data Collection Regarding Diet

Table 7. Reason for CD prevalence in Various Countries in Comparison to India

Reason	India	Africa	America	Australia	Finland
Asymptomatic Patients	✓	✓	✓	✓	✓
Lack of standardized tests	✓	✓	✓	✓	✓
Utility of Combination of Serological and Histological Test	✗	✗	✓	✓	✓
Lack of Non-invasive Confirmatory Test	✓	✓	✓	✓	✓
Co-existence of other diseases	✓	✓	✓	✓	✓
Intake of gluten frequently	✓	✓	✗	✗	✗
Availability/accessibility of confirmatory test in all the regions	✗	✗	✓	✓	✓

As the diet is an important factor for predisposal of celiac disease, hence a serious note of the diet pattern of the patient to be included in the samples for prevalence studies should be taken. The prevalence data has been

published by a number of scientists for different countries but in most of the studies, there was no information gathered regarding the diet of the sampled population. The information related to diet may also be a reason for the irrelevant diagnosis and inappropriate prevalence data.

Table 7 represents reasons for CD prevalence in various countries in comparison to India.

7. Conclusion

In the countries like India, the disease is enormously spreading and hence there is an urgent need to spread awareness regarding the disease, subtypes of CD including typical, atypical and silent subjects, various factors involved in disease generation etc. In conclusion, the prevalence of the disease is supposed to increase in the coming future and hence awareness regarding huge clinical spectrum of the celiac disease is mandatory. In addition, alertness amongst the physicians is desirable as the patients may possibly be false negative in the serological testing and disease may generate at later stages in the life. Sero-negative test result may indicate sero-positivity at some other time in the same population hence the factors such as diet etc must be taken into account while screening the celiac disease patients. Hence the physicians should vigilantly handle the probable patients. Apart it, free employment of serological/other screening tests must be warranted by the Government so that patients may be screened at early stages.

Till date either serological based tests or biopsy is being used for the diagnosis of the disease which is not approachable by underprivileged individuals. Hence simple and economical serological assays should be developed for studies. Moreover duodenal biopsy is being used for the confirmation of the disease. The major drawback of the duodenal biopsy is that it is an invasive and difficult technique with low degree of specificity. Hence, rapid and non-invasive tests should be designed for the timely and better diagnosis of the celiac disease patients. Novel and non-invasive methods of diagnosis will definitely be helpful in early detection of the disease that may have a direct impact in reducing childhood morbidity and mortality. Moreover, additional research and studying clinical parameters more deeply may be helpful to unfold other dimensions of the disease in India and abroad.

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Conflict of Interest and Ethical Standards

Authors have no conflict of interest.

References

[1] Ludvigsson JF, Leffler DA, Bai JC, Biagi F, Fasano A, Green PH, Hadjivassiliou M, Kaukinen K, Kelly CP, Leonard JN, Lundin KE. The Oslo definitions for coeliac disease and related terms, *Gut*, 2013, 62 (1). 43-52.

[2] Szebeni B, Veres G, Dezsofi A, Rusai K, Vannay Á, Bokodi G, Vásárhelyi B, Korponay-Szabó IR, Tulassay T, Arató A. Increased mucosal expression of Toll-like receptor (TLR) 2 and TLR4 in coeliac disease, *J Pediatr Gastroenterol Nutr*, 2007, 45 (2). 187-93.

[3] Di Sabatino A, Corazza GR. Coeliac disease, *The Lancet*, 2009, 373 (9673). 1480-93.

[4] Fasano, A., Catassi, C. Celiac disease. N Engl J Med 2012; 367: 2419-26.

[5] Tack GJ, Verbeek WH, Schreurs MW, Mulder CJ. The spectrum of celiac disease: epidemiology, clinical aspects and treatment, *Nat Rev Gastroenterol Hepatol* , 2010, 7. 204.

[6] Husby S, Koletzko S, Korponay-Szabo I Mearin M, Phillips A, Shamir R, et al. European Society for Pediatric Gastroenterology, Hepatology, and Nutrition guidelines for the diagnosis of coeliac disease, *J Pediatr Gastroenterol Nutr*, 2012, 54. 136-60.

[7] Van Belzen M, Koeleman B, Crusius J, Meijer J, Bardoel A, Pearson P, et al. Defining the contribution of the HLA region to cis DQ2-positive coeliac disease patients, *Genes and immunity*, 2004, 5. 215.

[8] Fasano A, Catassi C. Current approaches to diagnosis and treatment of celiac disease: an evolving spectrum, *Gastroenterology*, 2001, 120. 636-51.

[9] Lohi S, Mustalahti K, Kaukinen K, Laurila K, Collin P, Rissanen H, et al. Increasing prevalence of coeliac disease over time, *Aliment Pharmacol Ther* , 2007, 26. 1217-25.

[10] Celiac Disease Foundation. https: //celiac.org/about-celiac-disease/symptoms-of-celiac-disease/Symptoms of Celiac Disease. Accessed 11 jan 2019.

[11] Malekzadeh R, Sachdev A, Ali AF. Coeliac disease in developing countries: middle East, India and North Africa, *Best practice & research, Clin Gastroenterol*, 2005, 19. 351-8.

[12] Singh P, Arora A, Strand TA, Leffler DA, Catassi C, Green PH, et al. Global prevalence of celiac disease: systematic review and meta-analysis, *Clin Gastroenterol Hepatol*, 2018, 16. 823-36.

[13] Sood A, Midha V, Sood N, Avasthi G, Sehgal A. Prevalence of celiac disease among school children in Punjab, North India, *J Gastroenterol Hepatol*, 2006, 21. 1622-5.

[14] Ertekin, V., Selimoglu, M.A., Kardas, F., Aktas, E. Prevalence of celiac disease in Turkish children, *J Clin Gastroenterol*, 2005, 39. 689-91.

[15] Lohi S, Mustalahti K, Kaukinen K, Laurila K, Collin P, Rissanen H, Lohi O, Bravi E, Gasparin M, Reunanen A, Mäki M. Increasing prevalence of coeliac disease over time, *Aliment Pharm Ther*, 2007, 26 (9). 1217-25.

[16] Singh P, Arora A, Strand TA, Leffler DA, Catassi C, Green PH, Kelly CP, Ahuja V, Makharia GK. Global prevalence of celiac disease: systematic review and meta-analysis, *Clin Gastroenterol Hepatolo*, 2018, 16 (6), 823-36.

[17] Gujral N, Freeman HJ, Thomson AB. Celiac disease: prevalence, diagnosis, pathogenesis and treatment, *World J Gastroenterol*, 2012, 18 (42). 6036.

[18] Mustalahti, K., Catassi, C., Reunanen, A., Fabiani, E., Heier, M., McMillan, S., et al. The prevalence of celiac disease in Europe: results of a centralized, international mass screening project, *Ann Med*, 2010, 42. 587-95.

[19] Fasano A, Berti I, Gerarduzzi T, et al. Prevalence of celiac disease in at-risk and not-at-risk groups in the United States: a large multicenter study, *Arch Int Med*, 2003, 163. 286-92.

[20] Ivarsson A, Myle´us A, Norstro¨m F, et al. Prevalence of childhood celiac disease and changes in infant feeding, *Pediatrics*, 2013, 131. e687-94.

[21] White LE, Merrick VM, Bannerman E, et al. The rising incidence of Celiac Disease in Scotland, *Pediatrics*, 2013, 132. e924-31.

[22] Catassi C, Kryszak D, Bhatti B, et al. Natural history of celiac disease autoimmunity in a USA cohort followed since 1974, *Ann Med*, 2010, 42. 530-538.

[23] Yap TW-C, Chan W-K, Leow AH-R, et al. 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.

[24] Yap TW, Chan WK, Leow AH, et al. 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 (3). e0121908.

[25] Cummins AG, Roberts-Thomson IC. Prevalence of celiac disease in the Asia-Pacific region, *J Gastroenterol Hepatol*, 2009, 24 (8). 1347-1351.

[26] Hariz MB, Laadhar L, Kallel-Sellami M, et al. Celiac disease in Tunisian children: a second screening study using a "new generation" rapid test, *Immunol Invest* , 2013, 42. 356-368.

[27] Ben Hariz M, Kallel-Sellami M, Kallel L, et al. Prevalence of celiac disease in Tunisia: mass-screening study in schoolchildren, *Eur J Gastroenterol Hepatol*, 2007, 19. 687-694.

[28] Abu-Zekry M, Kryszak D, Diab M, et al. Prevalence of celiac disease in Egyptian children disputes the east-west agriculture dependent spread of the disease, *J Pediatr Gastroenterol Nutr*, 2008, 47. 136-140.

[29] Alarida K, Harown J, Ahmaida A, et al. Coeliac disease in Libyan children: a screening study based on the rapid determination of anti-transglutaminase antibodies, *Dig Liver Dis*, 2011, 43. 688-691.

[30] Farahmand F, Mir-Nasseri MM, Shahraki T, et al. Prevalence of occult celiac disease in healthy Iranian school age children, *Arch Iran Med*, 2012, 15. 342-345.

[31] Al Hatlani MM. Prevalence of celiac disease among symptomfree children from the Eastern Province of Saudi Arabia, *Saudi J Gastroenterol*, 2015, 21. 367-371.

[32] Catassi C, Gatti S, Fasano A. The new epidemiology of celiac disease, *J Pediatr Gastroenterol Nutr*, 2014, 59. S7-9.

[33] Rewers M. Epidemiology of celiac disease: what are the prevalence, incidence, and progression of celiac disease?, *Gastroenterology*, 2005, 128 (4). S47-51.

[34] Cummins AG, Roberts-Thomson IC. Prevalence of celiac disease in the Asia-Pacific region, *J Gastroenterol Hepatol*, 2009, 24. 1347-51.

[35] Walia BN , Mehta S , Gupte SP . Coeliac disease, *Indian Pediatr*, 1972, 9. 16-19 .

[36] Walia BN, Sidhu JK, Tandon BN, Ghai OP, Bhargava S. Coeliac disease in North Indian children, *Br Med J*, 1966, 2 (5524). 1233.

[37] Nelson R, McNeish AS, Anderson C. Coeliac disease in children of Asian immigrants, *The Lancet*, 1973, 301 (7799). 348-50.

[38] Khoshoo V, Bhan MK, Jain R, Phillips AD, Walker-Smith JA, Unsworth DJ, Stintzing G. Coeliac disease as cause of protracted diarrhoea in Indian children, *The Lancet*, 1988, 331 (8577). 126-7.

[39] Khoshoo V, Bhan MK, Unsworth DJ, Kumar R, Walker JS. Anti-reticulin antibodies: useful adjunct to histopathology in diagnosing celiac disease, especially in a developing country, *J Pediatr Gastroenterol Nutr*, 1988, 7 (6). 864-6.

[40] Catassi C, Gatti S, Lionetti E. World perspective and celiac disease epidemiology, *Digestive Dis*, 2015, 33 (2). 141-6.

[41] Bhattacharya M, Dubey AP, Mathur NB. Prevalence of celiac disease in north Indian children, *Indian Pediatrics*, 2009, 46 (5). 415.

[42] Walia BN, Sidhu JK, Tandon BN, Ghai OP, Bhargava S. Coeliac disease in North Indian children, *B Medl Jl*, 1966, 2 (5524). 1233.

[43] Puri AS, Garg S, Monga R, Tyagi P, Saraswat MK. Spectrum of atypical celiac disease in North Indian children, Indian Pediatrics, 2004, 41 (8). 822-6.

[44] Sood A, Midha V, Sood N, Avasthi G, Sehgal A. Prevalence of celiac disease among school children in Punjab, *North India. J Gastroenterol Hepatol*, 2006, 21 (10), 1622-5.

[45] 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 (5), 894-900.

[46] Ramakrishna BS, Makharia GK, Chetri K, Dutta S, Mathur P, Ahuja V, Amarchand R, Balamurugan R, Chowdhury SD, Daniel D, Das A. Prevalence of adult celiac disease in India: regional variations and associations, *Am J Gastroenterol*, 2016, 111 (1). 115.

[47] Green PH, Cellier C. Celiac disease, *N Engl J Med*, 2007, 25, 357 (17). 1731-43.

[48] Petronzelli F, Bonamico M, Ferrante P, et al. Genetic contribution of the HLA region to the familial clustering of coeliac disease, *Ann Hum Genet*, 1997, 61. 307-317.

[49] Hogberg L, Falth-Magnusson K, Grodzinsky E, Stenhammar L. Familial prevalence of coeliac disease: a twenty-year follow-up study, *Scand J Gastroenterol*, 2003, 38. 61-65.

[50] Almeida PL, Gandolfi L, Modelli IC, Martins RD, Almeida RC, Pratesi R. Prevalence of celiac disease among first degree relatives of Brazilian celiac patients, *Arquivos De Gastroenterologia*, 2008, 45 (1). 69-72.

[51] Bourgey MM, Calcagno GG, Tinto NN, Gennarelli DD, Margaritte-Jeannin PP, Greco LL, Limongelli MG, Esposito OO, Marano CC, Troncone RR, Spampanato AA. HLA-related genetic risk for coeliac disease, *Gut*, 2007, 56, 1037-1037.

[52] Hadithi M, von Blomberg BM, Crusius JB, Bloemena E, Kostense PJ, Meijer JW, Mulder CJ, Stehouwer CD, Pena AS. Accuracy of serologic tests and HLA-DQ typing for diagnosing celiac disease, *Ann Intern Med*, 2007, 147 (5). 294-302.

[53] Singla S, Kumar P, Singh P, Kaur G, Rohtagi A, Choudhury M. HLA Profile of Celiac Disease among First-Degree Relatives from a Tertiary Care Center in North India, *Indian J Pediatr*, 2016, 83 (11). 1248-1252.

[54] Maki M, Holm K, Hallstrom O, Collin P, Viander M, Savilahti E, Lipsanen V, Koskimies S. Serological markers and HLA genes among healthy first-degree relatives of patients with coeliac disease, *The Lancet*, 1991, 338 (8779). 1350-1353.

[55] Fasano A, Berti I, Gerarduzzi T, Not T, Colletti RB, Drago S, Elitsur Y, Green PH, Guandalini S, Hill ID, Pietzak M. Prevalence of celiac disease in at-risk and not-at-risk groups in the United States: a large multicenter study, *Arch Intern Med*, 2003, 163 (3). 286-292.

[56] Almeida PL, Gandolfi L, Modelli IC, Martins RD, Almeida RC, Pratesi R. Prevalence of celiac disease among first degree relatives of Brazilian celiac patients, *Arq Gastroenterol*, 2008, 45 (1). 69-72.

[57] Dogan Y, Yldrmaz S, Özercan IH. Prevalence of celiac disease among first-degree relatives of patients with celiac disease, *J Pediatr Gastroenterol Nutr*, 2012, 55 (2). 205-208.

[58] Bonamico M, Ferri M, Mariani P, Nenna R, Thanasi E, Luparia RP, Picarelli A, Magliocca FM, Mora B, Bardella MT, Verrienti A. Serologic and genetic markers of celiac disease: a sequential study in the screening of first degree relatives, *J Pediatr Gastroenterol Nutr*, 2006, 42 (2). 150-154.

[59] Tursi A, Elisei W, Giorgetti GM, Gaspardone A, Lecca PG, Di Cesare L, Brandimarte G. Prevalence of celiac disease and symptoms in relatives of patients with celiac disease, *Eur Rev Med Pharmacol Sci*, 2010, 14 (6). 567-572.

[60] Mishra A, Prakash S, Kaur G, Sreenivas V, Ahuja V, Gupta SD, Makharia GK. Prevalence of celiac disease among first-degree relatives of Indian celiac disease patients, *Dig Liver Dis*, 2016, 48 (3). 255-259.

[61] Srivastava A, Yachha SK, Mathias A, Parveen F, Poddar U, Agrawal S. Prevalence, human leukocyte antigen typing and strategy for screening among Asian first-degree relatives of children with celiac disease, *J Gastroenterol Hepatol*, 2010, 25 (2). 319-324.

[62] Uenishi RH, Gandolfi L, Almeida LM, Fritsch PM, Almeida FC, Nóbrega YK, Pratesi R. Screening for celiac disease in 1st degree relatives: a 10-year follow-up study, *BMC Gastroenterol*, 2014, 14 (1). 36-39.

[63] Cosnes J, Cellier C, Viola S, Colombel JF, Michaud L, Sarles J, Hugot JP, Ginies JL, Dabadie A, Mouterde O, Allez M. Incidence of autoimmune diseases in celiac disease: protective effect of the gluten-free diet, *Clin Gastroenterol Hepatol*, 2008, 6 (7). 753-758.

[64] Levitsky LL, Misra M. Associated autoimmune diseases in children and adolescents with type 1 diabetes mellitus. *Up To Date*, 2007, 17. 23-26.

[65] Bardella MT, Elli L, Matteis SD, Floriani I, Torri V, Piodi L. Autoimmune disorders in patients affected by celiac sprue and inflammatory bowel disease, *Annals Med*, 2009, 41 (2). 139-143.

[66] Ventura A, Magazzù G, Greco L. Duration of exposure to gluten and risk for autoimmune disorders in patients with celiac disease, *Gastroenterology*, 1999, 1, 117 (2). 297-303.

[67] Roy A, Laszkowska M, Sundström J, Lebwohl B, Green PH, Kämpe O, Ludvigsson JF. Prevalence of celiac disease in patients with autoimmune thyroid disease: a meta-analysis, *Thyroid* 2016, 26 (7). 880-890.

[68] Dogan B, Oner C, Bayramicli OU, Yorulmaz E, Feyizoglu G, Oguz A. Prevalence of celiac disease in adult type 1 patients with diabetes, *Pakistan J Med Sci*, 2015, 31 (4). 865-867.

[69] Watanabe C, Hokari R, Komoto S, Tomita K, Ogata S, Miura S. Sa1318 Prevalence of Celiac Disease in Patients With Inflammatory Bowel Disease: A Study From Japan, *Gastroenterology*, 2012, 142 (5). S-271.

[70] Coaccioli S, Landucci P, Fatati G, Del Giorno R, Papini M, Puxeddu A. Prevalence of coeliac disease in rheumatoid and psoriatic arthritis and in psoriasis, *J Clin Endocrinol Metab*, 2010, 3 (1). 61-64.

[71] Najafi M, Sadjadei N, Eftekhari K, Khodadad A, Motamed F, Fallahi GH, Farahmand F. Prevalence of Celiac Disease in Children with Autoimmune Hepatitis and vice versa, *Iranian J Ped*, 2014, 24 (6). 723-725.

[72] Rodrigo L, Hernández-Lahoz C, Fuentes D, Alvarez N, López-Vázquez A, González S. Prevalence of celiac disease in multiple sclerosis, *BMC Neuro*, 2011, 11 (1). 31-35.

[73] Rutz R, Ritzler E, Fierz W, Herzog D. Prevalence of asymptomatic celiac disease in adolescents of eastern Switzerland, *Swiss Med Wkly*, 2002, 132 (3-4). 43-47.

[74] Lo W, Sano K, Lebwohl B, Diamond B, Green PH. Changing presentation of adult celiac disease, *Dig Dis Sci*, 2003, 48 (2). 395-398.

[75] Volta U, Villanacci V. Celiac disease: diagnostic criteria in progress, *Cell Mol Immunol*, 2011, 8 (2). 96.