Gastroenterology in Arab Countries

Seroprevalence of coeliac disease in at-risk subjects at the main tertiary hospital, southwest of Saudi Arabia

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Abstract
Background and study aims: Coeliac disease (CD) is a gluten-induced autoimmune inflammation of small bowel villi, leading to atrophy and malabsorption. The current study aims to assess the prevalence of CD in high-risk subjects in the Aseer region, southwest of Saudi Arabia and to investigate the associated presentations.

Patients and methods: This is a retrospective case-finding study of the laboratory records for a 3-year period (2009–2012) at the main tertiary hospital (Aseer Central Hospital). Serum anti-tissue transglutaminase (atTG) and endomysial antibody (EmA) levels were determined along with small intestinal histopathological examination.

Results: The proportion of cases that tested positive for at least one coeliac antibody marker was 18.4% (58/315). Forty cases underwent endoscopic examination during the analysis, among which 22 were confirmed to have CD. The individual antibody positivity for atTG and EmA was 17.5% and 15.6%, respectively. The most common clinical condition (47%) associated with these markers was type 1 diabetes mellitus (T1DM). Interestingly, gastrointestinal presentations constituted only 11.5%.

Conclusions: The rate of CD among hospital requests, including non-gastrointestinal symptomatic patients, at the Aseer main tertiary hospital seems to be high. Determining the prevalence of CD and also investigating the high-risk group commonly affected by CD warrant more screening studies.

Introduction
Coeliac disease (CD) is an autoimmune disorder triggered by ingestion of the gluten protein that causes damage to the small intestinal mucosa, thereby leading to malabsorption and gastrointestinal complications [1]. This disease is often underdiagnosed as several cases are missed in clinical settings [2], as typical presentation of symptomatic diarrhoea and abdominal pain. However, unusual presentations such as short stature, failure to thrive (FTT), anaemia, and calcium and vitamin deficiency were counted in high percentages of disease presentations [3]. Furthermore, autoimmune diseases such as type 1 diabetes and autoimmune thyroiditis are associated with an increased incidence of CD [4–6]. Recent categorisation of this disease presentation by the European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHN) divides them into gastrointestinal and extra-intestinal symptoms and signs – silent, latent, and potential – conveying how common diseases exist in the absence of apparent symptoms [7,8].

With the advent of various serological screening antibodies such as anti-human tissue transglutaminase (atTG) and endomysial antibody (EmA), diagnosis of CD has improved, but duodenal biopsy still remains a cornerstone in the diagnosis of CD [9]. The European society of CD has approved positive serological markers for both atTG and EmAs in addition to HLA DQ2 or DQ8 as a diagnostic for CD [10,11]. In general, CD antibody detection is the less invasive and most suitable method for primary investigation of CD in suspected subjects and for assessing disease prevalence.

In contrast to that previously assumed about the prevalence of CD (0.03%) [3], the more recent studies showed a high prevalence of this disease (1%) in some European countries and the United States [12–14]. CD prevalence varies from one area to another according to the genetic and environmental factors. For example, the prevalence of CD in Saharawi children was confirmed by intestinal biopsies with serological markers to be 5.6% [15]. Studies in Saudi Arabia showed some degree of variation, with prevalence in school-age children and healthy adults shown as much as 1.5–2.2% [16,17]. Conversely, the percentage of symptomatic or high-risk patients varies from 4% in symptomatic to 11% in type 1 diabetes mellitus (T1DM) individuals [18,19]. However, such variations can be attributed to difference in the methodology and the targeted age groups, and both genetic and environmental factors cannot be excluded.

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The aim of this study is to investigate the prevalence of CD and to describe the associated presentations among at-risk individuals attending the main tertiary hospital in Aseer region, a southwestern area of Saudi Arabia.

**Patients and methods**

This is a hospital-based retrospective study conducted at Aseer Central Hospital, a tertiary and the main reference hospital for Aseer region, a southwestern area of Saudi Arabia. A total of 313 patient files were obtained from the medical records department, where requests of CD markers were ordered. The data obtained during the period from July 2009 to September 2012 were analysed for patient demographics, symptoms, coeliac antibodies, atTG, EmAs, and intestinal histopathological findings.

The main presentations such as chronic diarrhoea or abdominal pain or (and the reason of requests such as T1DM, thyroid disease, FTT, short stature, anaemia, and associated neurological diseases constituted the inclusion criteria. Coeliac profile was requested routinely for most of T1DM, thyroid diseases, short stature, and FTT as well as chronic abdominal symptomatic patients.

The diagnosis of CD is based on the specific antibody detection and histopathological findings of intestinal biopsy. Antibodies used were anti-tissue transglutaminase A antibody test (atTG-A; Immco diagnostics, Buffalo, NY, USA) with a cutoff value of 50 EU/ml, anti-tissue transglutaminase G antibody test (atTG-G; Immco diagnostic, Buffalo, NY, USA) and endomyosal antibodies (EmA; Immco diagnostic, Buffalo, NY, USA).

Histopathological examination was conducted to visualise the typical characteristic features of crypts, atrophy of villi, and intraepithelial lymphocytosis. Changes were reported by pathologists according to Marsh classification [8,10]. Histopathological data were missing for some patients due to an incomplete follow-up. Some patients might visit alternative private or abroad hospitals.

Data were analysed using the Statistical Package for Social Sciences programme (SPSS; Version 16). All p-values < 0.05 were considered statistically significant.

**Results**

Out of 315 (139 male and 176 female) individuals, 58 (18.4%; 18 (13%) men and 40 (22.7%) women) tested positive for at least one antibody marker; a significantly increased positivity was observed in female patients (p < 0.05). The median age of the study population was 10 years (range: 1–79 years; SD ± 10.6). Antibody markers used for CD diagnosis during the study periods were atTG and EmA. Among 268 atTG tests performed in the study period 47 (17.5%) cases tested positive, whilst 17 (15.6%) tests showed a positive result for 109 cases of anti-EmA (Table 1). Further assessment of atTG-IgG (immunoglobulin G) levels was performed concomitant with IgA levels. Eleven atTG-IgG-positive patients tested negative for atTG-IgA; nine showed low positive atTG-IgA titre whilst one was moderate. Only one patient was found to be strong atTG-IgG positive and tested negative for atTG-IgA levels. Both moderate and strong IgG-positive samples tested negative for EmA. The duodenal histopathological results of only 40 cases could be derived within the study time period. Out of these 40 cases, 22 cases were confirmed for CD and six showed intestinal abnormalities with no confirmatory changes of CD, whilst 12 showed normal intestinal mucosa. The results of the six suspicious cases showed that two of them showed low positive atTG-IgA titre with intestinal abnormalities (March-II). Only one sample tested positive for atTG-IgA and EmA with normal intestinal mucosa (Table 1).

Clinical presentations of patients varied from classical gastrointestinal symptoms such as chronic diarrhoea and abdominal pain to nonclassical symptoms such as endocrine and neurological diseases. During the study period, T1DM was the most prevalent clinical condition in about half (46.5%) of the requested cases. About 4.5% of the patients with T1DM had hypothyroidism, whilst 3.7% had only hypothyroidism. The other clinical diagnostic data for CD markers included FTT (11.9%) and short stature (6.6%). Gastrointestinal presentations such as abdominal pain and chronic diarrhoea were observed only in 11.5% of the requested cases. Other non-categorised conditions included anaemia, neurological symptoms, Down syndrome, and rickets which accounted for the rest of the cases (Table 2).

T1DM was the most common clinical condition among CD-positive patients. In general, about 30 (22.9%) of 131 cases of T1DM were positive for any single antibody test. Specifically,

### Table 1

The frequencies of coeliac disease among high-risk subjects. Serology results (in the first row) are recorded for any coeliac markers used in the time period (atTG-A and EmA). Lower rows show different coeliac markers used for coeliac disease diagnosis. The columns in the right side indicate the number of positive cases for each test out of the tested cases. More than one antibody test was used in some of the cases.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Number of cases</th>
<th>Positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>General results</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serology</td>
<td>315 (139 m/176 f)</td>
<td>58 (18.4%)</td>
</tr>
<tr>
<td>Histopathology</td>
<td>22</td>
<td>9.9%</td>
</tr>
<tr>
<td>Specific antibodies and histopathology results</td>
<td></td>
<td></td>
</tr>
<tr>
<td>atTG-A</td>
<td>268</td>
<td>47 (17.5%)</td>
</tr>
<tr>
<td>EmA</td>
<td>109</td>
<td>17 (15.6%)</td>
</tr>
<tr>
<td>V. Atrophy</td>
<td>40</td>
<td>22 (55%)</td>
</tr>
</tbody>
</table>

### Table 2

Reason for coeliac disease requests in Aseer Central Hospital for a three-year period. Total number of the files reviewed was 315; only in 243 files the reason for the request was stated. Others (in row number 9) include epilepsy, Ricket’s, anorexia nervosa, Bartter’s syndrome, Down syndrome, Turner syndrome, and SLE with lupus nephritis.

<table>
<thead>
<tr>
<th>No</th>
<th>Reason for request</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>T1DM</td>
<td>113</td>
<td>46.5</td>
</tr>
<tr>
<td>2</td>
<td>T1DM + Hypothyroid</td>
<td>11</td>
<td>4.5</td>
</tr>
<tr>
<td>3</td>
<td>Hypothyroid</td>
<td>9</td>
<td>3.7</td>
</tr>
<tr>
<td>4</td>
<td>Short stature</td>
<td>16</td>
<td>6.6</td>
</tr>
<tr>
<td>5</td>
<td>Failure to thrive</td>
<td>29</td>
<td>11.9</td>
</tr>
<tr>
<td>6</td>
<td>Abdominal pain</td>
<td>16</td>
<td>6.6</td>
</tr>
<tr>
<td>7</td>
<td>Chronic diarrhoea</td>
<td>12</td>
<td>4.9</td>
</tr>
<tr>
<td>8</td>
<td>Anaemia</td>
<td>8</td>
<td>3.3</td>
</tr>
<tr>
<td>9</td>
<td>Others</td>
<td>29</td>
<td>11.9</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>243</td>
<td>100</td>
</tr>
</tbody>
</table>

### Table 3

Positives among the reasons for request. The most common positive cases are type 1 diabetes (T1DM).

<table>
<thead>
<tr>
<th>Reason for request</th>
<th>Any Pos.</th>
<th>atTG-A</th>
<th>EMA</th>
<th>V. atrophy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of cases and %</td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>1</td>
<td>T1DM</td>
<td>30</td>
<td>51.7</td>
<td>24</td>
</tr>
<tr>
<td>2</td>
<td>T1DM + Hypothyroid</td>
<td>2</td>
<td>3.5</td>
<td>2</td>
</tr>
<tr>
<td>3</td>
<td>Hypothyroid</td>
<td>1</td>
<td>1.7</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>Short stature</td>
<td>2</td>
<td>3.5</td>
<td>2</td>
</tr>
<tr>
<td>5</td>
<td>Failure to thrive</td>
<td>3</td>
<td>5.2</td>
<td>3</td>
</tr>
<tr>
<td>6</td>
<td>Abdominal pain</td>
<td>4</td>
<td>6.9</td>
<td>4</td>
</tr>
<tr>
<td>7</td>
<td>Chronic diarrhoea</td>
<td>1</td>
<td>1.7</td>
<td>1</td>
</tr>
<tr>
<td>8</td>
<td>Anaemia</td>
<td>2</td>
<td>3.5</td>
<td>2</td>
</tr>
<tr>
<td>9</td>
<td>Others</td>
<td>6</td>
<td>10.3</td>
<td>5</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>51</td>
<td>43</td>
<td>15</td>
</tr>
</tbody>
</table>

All positive cases for any antibody marker as shown are 58, but in some positive; data of the main presentations are missing in the reviewed records.
24 (21.6%) of 111 cases with T1DM tested positive for atTG-IgA antibody test. Twelve (27%) of 43 T1DM cases tested positive for antibody EmA; five cases were histopathologically diagnosed with CD, and three ambiguous cases out of eight T1DM underwent endoscopic examinations during the study (Table 3).

Discussion

Coeliac Disease is a chronic immune-mediated disorder of the intestine that manifests in response to ingestion of gluten-rich food [1]. CD was previously considered a rare disease (1:8000), whilst recent studies estimate the prevalence of the disease to be around 1:100. The rate of missing cases is eight times higher than that diagnosed, in addition to the delay in diagnosis up to 13 years in average [2]. Despite several advancements with regard to sensitive serological tests, the actual disease prevalence remains improbable and the disease is still underdiagnosed [20]. In the current study, we investigate CD prevalence in at-risk subjects through analysis of the requested cases for a 3-year period in a tertiary hospital of the Aseer region. Of all the requested cases, 18.4% showed positive serology results, whilst 5.4% cases were histopathologically confirmed. In addition, the presence of positive cases in different age groups and requesting of non-symptomatic patients indicate a good awareness about CD among physicians.

Further prevalence of CD among high-risk people in the Aseer region has not been addressed earlier. Besides, the clinical condition associated with CD in this area is unknown. The results showed a gross positivity about 15–18% with different serological markers in the requested cases. Although atTG-IgA and EMA showed high sensitivity and specificity for CD screening, histopathological confirmation results in a 3-year period showed that 22 (6.9%) cases out of 315 files represent a high proportion significant to alert the clinical practitioners about the rise of CD in the Aseer region. A similar study conducted in Jeddah, western Saudi Arabia, showed 80 confirmed cases over a 5-year retrospective review of all coeliac requested markers [21]. Furthermore, a study in western Saudi Arabia showed the prevalence of CD in about 7.6% of patients [20]. Apart from at-risk or symptomatic patients, screening for 1167 school children of age 14–17 years from three different regions of Saudi Arabia including Aseer showed CD prevalence of 2.1% and a positivity of 3.1% in Al-Qaseem [17]. Another study in the western region of Saudi Arabia showed that about 1.5% of 204 adult healthy participants tested positive for CD during serological testing of blood donors [16]. This could suggest that the estimated number of CD cases in this region and, in general, in Saudi Arabia might be higher and there is a need for screening strategy to address the real prevalence of this disease. A North American study for at-risk subjects showed that only 2.25–4.5% tested positive for CD [22,23], and the general worldwide prevalence estimation is about 1% [1]. Determining the rate of prevalence of this disease in Saudi Arabia necessitates a study in a large population.

The data accumulated showed the reliability and specificity of serological tests in the diagnosis of CD. The evidence-based guidelines and criteria of European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) for the diagnosis of CD suggest the use of serological testing in determining atTTG and EmAs in addition to HLA typing [10,24]. Although histopathological findings still serve as the main confirmatory tool, many studies revealed that some intestinal changes could be missed due to focal intestinal changes in addition to low-skilled biopsies that can interfere with test sensitivity [25]. In addition, it is easier to perform screening and detection of CD using serological markers as they are less invasive and cost-effective. Hence, majority of the studies were based on results obtained with regard to atTTG and EmA levels. Several limitations such as the use of anti-gliadin antibodies (AGAs) and poor patient follow-up after positive serological test make the results less competent. The AGA test is no longer recommended for CD screening due to its low specificity, and it has been included in the hospital records. This test had been previously conducted in the hospital; however, the current strategy employed includes testing of atTTG and EmA levels. The serological tests were followed by duodenal biopsies to confirm the diagnosis.

CD screening revealed the variations in the disease manifestation in terms of silent, minor, or major symptoms. In addition, studies explored the association of CD with other autoimmune diseases and increased the disease awareness in those patients [5,26]. In the current study, we retrospectively study the records to determine the prevalence of CD in the region. Interestingly, majority of positive coeliac antibodies were found in non-gastrointestinal symptomatic patients.

In the coeliac marker requested cases, T1DM was found to be the most common clinical condition, yielding the highest positive results. A study conducted in Riyadh showed that CD positivity among T1DM patients was 19 out of 106 children [18]. FTT and short stature represented the second most common presentation followed by chronic abdominal pain. Recent studies in Riyadh have addressed FTT and short stature as a consequence of CD. Patients presented with unexplained short stature; the rate of prevalence of rickets and CD was 10–14% and 38%, respectively [27,28]. The number of cases presenting with short stature and rickets in the current study was rather low; however, we might have missed this information as this study is only a retrospective evaluation.

The ease and availability of screening tools for CD, along with the rising awareness of silent, latent, and potential patient of this disease, will result in a greater portion of the population constituting the submerged part of the ‘iceberg’ being diagnosed.

In conclusion, this study showed a high rate of prevalence of CD among hospital record cases in Aseer main tertiary hospital. It also highlighted the need for screening among non-gastrointestinal symptomatic patients and patients who suffer from autoimmune diseases especially children with T1DM. Detection of the actual rate of prevalence of the disease requires a study involving a large population for establishing a national awareness programme regarding CD.

Conflict of interest

The author declare that he has no conflict of interest in this study.

References


