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# Clinical Picture of Celiac disease: Experience from a health care provider in Arabia

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### ABSTRACT

**Background:** Most studies describing clinical features and associations of celiac disease come from the studies conducted in the western world. Our aim was to determine the clinical features and associations of Celiac disease from our centre serving a Middle East population in Saudi Arabia.

**Methods:** This retrospective study was conducted in a health care provider serving the Eastern Province of Saudi Arabia. All patients with biopsy-confirmed celiac disease receiving health care at our centre between April 2002 and December 2018 were identified. Individual case records were reviewed. In addition, the Slicer Dicer function was also used from the Electronic medical health record [EPIC] for analysing the clinical features and associations.

**Results:** We analyzed the clinical features of 149 patients with Celiac disease. 66% of these were females. There was progressively increased yield of confirmed Celiac disease over the study period. This was paralleled by an increase in TTG antibody tests performed year by year. 77 (51.6%) patients had gastrointestinal symptoms. 26% of patients had iron deficiency anemia. 24 patients (16%) had diabetes, of which 46% were type 2. 18 (12%) patients had osteoporosis or osteopenia, and 28 (19%) had various skin diseases.

**Conclusion:** In Saudi Arabia, celiac disease is being increasingly recognized, largely because of increased awareness and increasing TTG antibody testing. Many patients present with non-gastrointestinal symptoms. Knowledge about the varied clinical features and the targeted use of celiac serology should lead to even earlier recognition of the disease.

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## Introduction

Celiac disease is reported worldwide <sup>1</sup>. It is an autoimmune disease seen in genetically predisposed people by the consumption of food containing gluten. The classical signs of Celiac disease include symptoms of malabsorption, including diarrhea, steatorrhea, and weight loss or growth failure. Often patients are largely devoid of gastrointestinal symptoms and have non-classical presentation. Such patients have symptoms like abdominal pain, abdominal bloating, chronic migraine, peripheral neuropathy, anemia etc. In the absence of typical diarrheal presentation, many patients with celiac disease may not be tested and hence left undiagnosed. Establishing the diagnosis of celiac disease is important due to the danger of nutritional deficiencies, low birth weight infants of affected mothers, and increased occurrence of autoimmune diseases and malignancies with ongoing gluten containing diet. The literature suggests an increasing trend of atypical, or non-classical celiac disease <sup>2</sup>.

While there is evidence that there is a true increase in the incidence of celiac disease <sup>3</sup>, the increasing number of serologic tests being performed also contribute to the increased recognition of cases.

The worldwide pooled prevalence based on serology (seroprevalence) is believed to be around 1.4% and pooled global prevalence of biopsy confirmed celiac disease is around 0.7% [95% confidence interval, 0.5% to 0.9%] <sup>4</sup>. However, the prevalence in the various geographical locations vary. In the Asian population, the prevalence was thought to be 0.6% <sup>4</sup>. Celiac disease was previously considered uncommon among the non-Caucasian populations. However, community-based studies from the Middle East have demonstrated that this condition indeed affects the Arab population <sup>5-10</sup>. There have been no studies looking at prevalence of biopsy proven Celiac disease from the Arabian Peninsula region. Although there is one study looking at the clinical features of celiac disease among 59

individuals in the pediatric age group from Saudi Arabia <sup>11</sup>, there are no studies in the Middle East and North Africa region (MENA) looking comprehensively at the clinical features of Celiac disease and associations in adult patients.

This study aimed at studying the clinical characteristics and reporting trend of all patients with biopsy confirmed Celiac disease between April 2002 and December 2018 in our center.

## Methods

All cases of celiac disease were identified retrospectively at our center, located in the eastern province of Saudi Arabia. The catchment population served by our health care organization come from various parts of Saudi Arabia and is relatively stable; most are Saudi nationals and are demographically representative of the country.

Ethical approval for the study was obtained from the institution review board (IRB) at Johns Hopkins Aramco Healthcare.

Cases of Celiac disease were identified using the laboratory serology database, the electronic medical health records (EPIC) and pathology reports at JHAH. Histologic diagnosis was in accordance with the modified Marsh Criteria <sup>12,13</sup>.

The laboratory department provided information on all the patients on their database who underwent TTG antibody tests from 1<sup>st</sup> April 2002 to December 31 2018. The calibrated reference ranges from the Mayo Clinic laboratory was used to identify positive tests. The pathology records stored in the electronic database were also accessed.

Patients with positive anti TTG test and had duodenal biopsies compatible with celiac disease were considered as confirmed case of Celiac disease. All patients who did not have confirmatory duodenal biopsies were excluded.

Clinical data was collected from the individual medical records of confirmed Celiac disease patients. The *Slicer Dicer* <sup>14</sup> function of the electronic health record (EPIC)<sup>15</sup> was also used

to gain additional clinical information about these patients.

Details regarding patient demographics, patient symptoms and associations with other medical conditions were recorded. The speciality of the physician making the initial diagnosis was determined from the test request forms.

The studied population included both children and adults. The paediatric subgroup consisted of those aged below 14 years at the time of serology testing. This reflects the practice at our center where patients less than 14 years of age are cared for by the paediatric department.

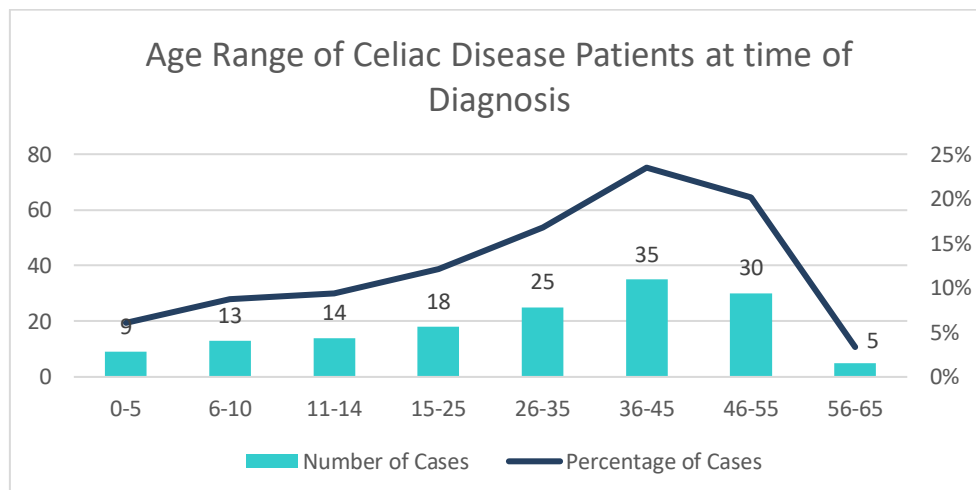
## Results

There were 149 patients identified to have biopsy confirmed Celiac disease. Of these, 101

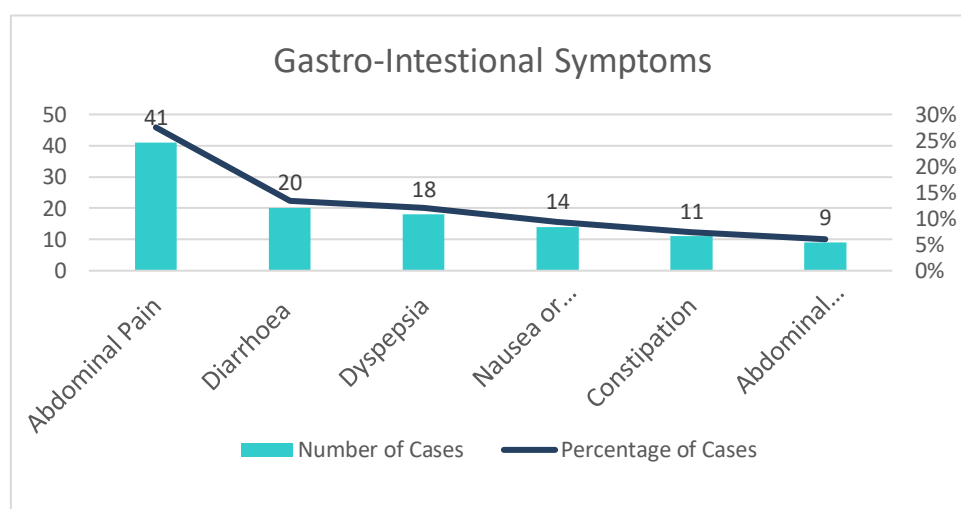
were female and 48 patients were male, giving a female to male ratio of 2:1. The ages at diagnosis are shown in figure 1. The median age at diagnosis among males was 34.7 years, range 1.4 to 63.7 years. Female patients had median age of 34.1 years (range 6.8 to 59.4 years). There were no significant differences between the two genders.

Most (83%) of the patients were Saudi Arabian nationals.

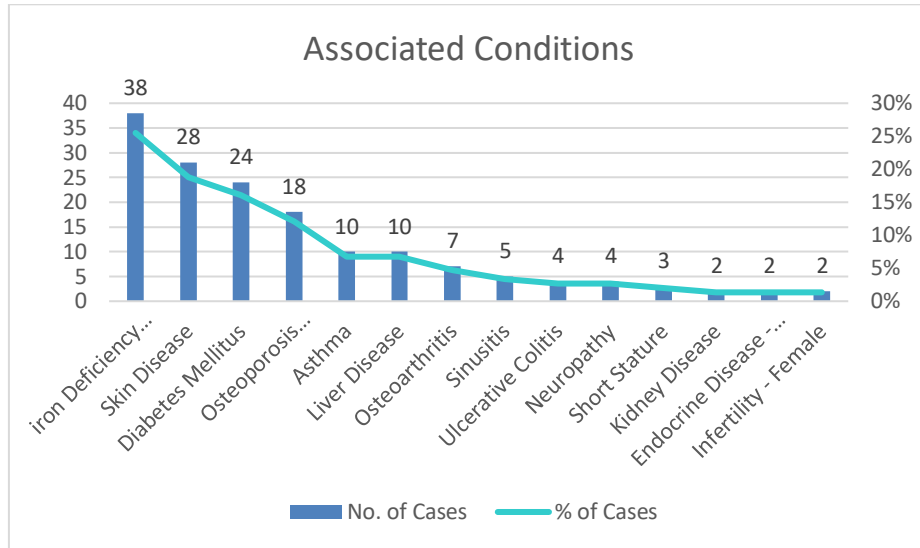
34 cases (23%) were children under the age of 14 years. 37.5% of cases were diagnosed between the age of 24 and 44 years of age. The oldest patient diagnosed to have celiac disease was 63.7 years of age.



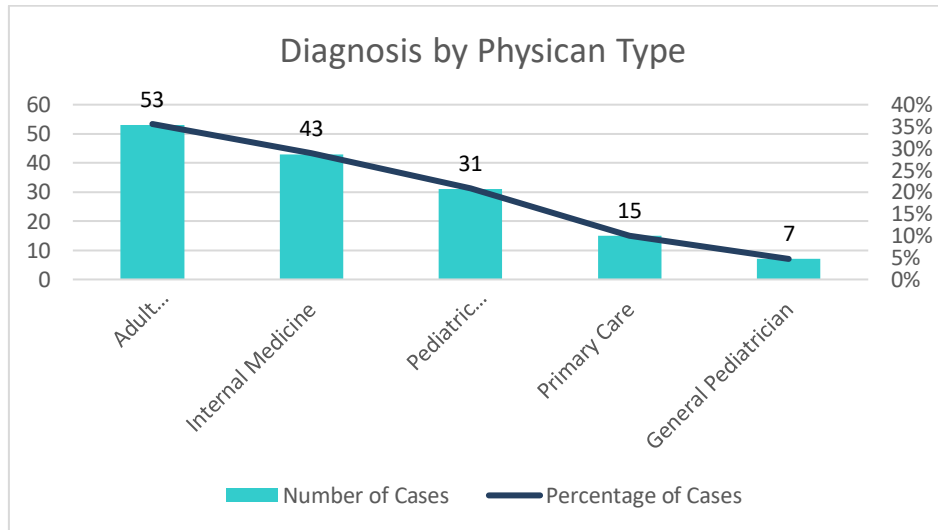
**Figure 1 Age of Diagnosis of Celiac Disease**



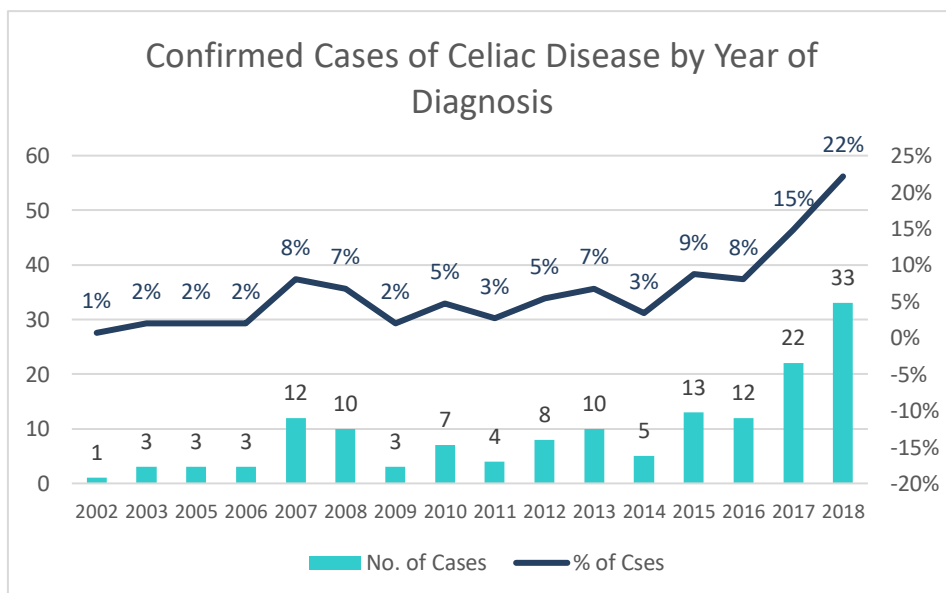
**Figure 2 Gastrointestinal symptoms**



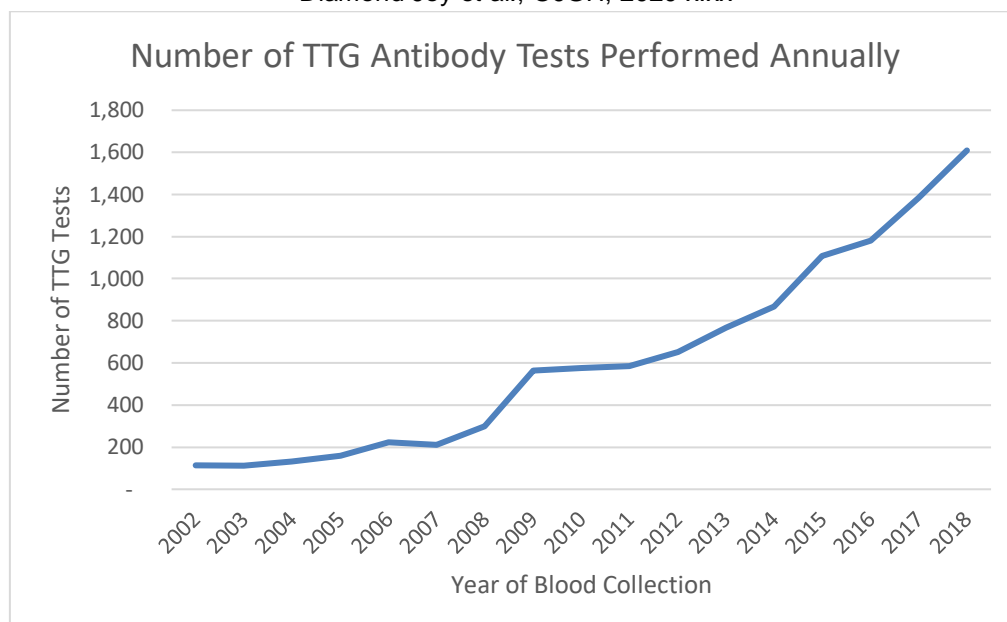
**Figure 3 Non Classical Clinical features of Celiac Disease**



**Figure 4 Physician making diagnosis of Celiac Disease**



**Figure 5 Confirmed cases of Celiac disease by year of diagnosis**



**Figure 6 Number of TTG antibody tests performed annually**

77 (51.6%) patients had one or more gastrointestinal symptom. They are listed in figure 2. The most common gastrointestinal symptom was abdominal pain (28.8%). Diarrhoea accounted for only 13% of the patients. 11 (7.3%) had the irritable bowel syndrome. 37 (24.8%) patients were completely asymptomatic

11 patients with Celiac disease (7.3%) had a diagnosis of Irritable bowel syndrome.

Many other conditions were found in our patients as shown in figure 3. One quarter of the patients had iron deficiency anaemia. Osteoporosis or osteopenia was found in 12%. 16% had diabetes, 46% of them being type 2.

Seven patients (4.7%) had a malignancy- of the breast in five, testis in one, and thyroid in one. One patient died aged 45 years with progressive weight loss of undermined cause.

84 (56%) patients were diagnosed by a gastroenterologist (either adult or paediatric) and 50 (33%) by other hospital physicians (either adult or paediatric). 15 (10%) were diagnosed in primary care. This is outlined in table 4.

The number of cases of celiac disease diagnosed each year is given in Figure 5, showing a dramatic increase over the 16 years of study - from one to 33. We have also shown

(figure 6) a roughly parallel increase in the number of TTG antibody tests performed at our center over the same period.

### Discussion

This is the largest study of celiac disease from a health care provider setting in the Middle East. Our study shows that Celiac disease is not an uncommon in either primary care or secondary care. The overall positivity rate of TTG antibody in our health care was 2.11%. It is to be noted that serology test was performed in health care provider setting and not among the general population. So the pre-test probability of positive test is expected to be higher than the general population.

The rate of diagnosis has increased markedly and progressively over the past 16 years, and this increase, paralleled by a progressively increased number of serological tests at our center, may be a reflection of greater awareness of the condition and increased serological testing. However, we cannot exclude the possibility of a real increase in the incidence of celiac disease<sup>3</sup>. It is also to be noted that there is also evidence in the literature of true increase in the prevalence of Celiac disease<sup>16</sup>.

Although just over half of our patients had one or more gastrointestinal symptom, features typical

of malabsorption were not common. Iron deficiency anaemia was found in a quarter of patients. It has been shown to be the commonest extraintestinal feature of celiac disease<sup>17</sup>. Around 5% patients with iron deficiency anaemia have celiac disease<sup>18</sup>. Various organizations like the World Gastroenterology Organization, North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN), European Society for the Study of Coeliac Disease, and British Society of Gastroenterology recommend testing for celiac disease in clinical situations with iron deficiency anaemia<sup>19–22</sup>. Our study supports testing for celiac disease in patients who have iron deficiency anaemia.

Diabetes was seen in 16% of patients. Although there is a well recognized association of diabetes with celiac disease<sup>23–26</sup>, it is usually type 1, whereas in this study 46% of the diabetics were type 2. While it might seem surprising to see patients with celiac disease having type 2 Diabetes mellitus, it is to be noted that this area in the MENA region has a high prevalence of Diabetes Mellitus<sup>27</sup>. The countrywide prevalence of type 2 Diabetes is around 25.4%<sup>28</sup> in Saudi Arabia which makes it among the top ten countries worldwide with highest prevalence of diabetes mellitus. In our study, 7% of the celiacs had type 2 diabetes mellitus which is lower than expected. This study population included children and less of people in the elderly age group; this could explain the lower rates of type 2 Diabetes mellitus when compared to general population figures. Therefore, presence of type 2 diabetes should not be taken as a reason for not screening for celiac disease. There has also been suggestion for screening for celiac disease in type 2 diabetes mellitus<sup>29,30</sup>. Osteoporosis or osteopenia which is also well recognized in celiac disease<sup>31</sup>, was seen in 12% of our patients. We found 19% of patients with skin disease, the type not being specified. Dermatitis herpetiformis is the only skin disease with a confirmed association with celiac disease – 75

to 80% having evidence of celiac disease<sup>21 32</sup>, but far fewer celiac disease patients (<5%) have dermatitis herpetiformis.

It is encouraging that non-gastroenterologist physician, both in hospital and primary care, are also diagnosing celiac disease, accounting for 44% of the cases.

This study benefits from a long study period of nearly 17 years. Our centre is unique in the respect that despite being based in eastern province, has catchment population of Saudi nationals coming from different parts of the country. Hence this population mix could be considered representative of the country.

We used two major databases to identify patients with celiac disease: Mayo clinic records of all the serology tests performed, and our electronic health records.

The benefits of early recognition of this condition are well known, helping to prevent disease related morbidity and mortality. Some of the celiac disease related complications such as osteoporosis and iron deficiency anemia are potentially preventable with adherence to a gluten free diet. Furthermore, undiagnosed Celiac disease patients who do not receive timely treatment have increased risk of developing autoimmune disorders and malignant cancers<sup>33</sup>.

There have been studies of general healthy asymptomatic population in the Middle East looking at the prevalence of positive TTG antibody tests which ranged 1.17% in the United Arab Emirates<sup>7</sup> to point prevalence of around 4% in other Arabian regions<sup>5,6,10</sup>.

A study in 2012 from Saudi Arabia has suggested that the prevalence rate of celiac disease among Saudi children with Type 1 diabetes is very high at 17.9%<sup>8</sup>. Our study supports the need for testing for Celiac disease among patients with endocrine conditions like diabetes and thyroid disease.

Our study shows that the number of cases of symptomatic celiac disease over the years is fewer than expected considering the prevalence

of celiac disease in studies from the Middle East among asymptomatic individuals. This is despite the increasing number of anti TTG tests being performed in our health care setting, thus reflecting an iceberg phenomenon.

This study has some limitations. Due to the retrospective nature of this study, some of the suspected cases of celiac disease with positive serology were lost to follow up and hence diagnosis could not be confirmed with duodenal histology. It is likely that a number of patients with celiac disease are left undiagnosed due to atypical clinical features. However, our study has a sizeable number of confirmed cases which should give a reliable reflection of the clinical features of this condition in this population.

A meta-analysis has shown that the ratio of known to unknown cases of Celiac disease in the community approaches 1: 7 which supports that detection rates needs to improve<sup>32,33</sup>.

The results certainly highlight the need for awareness of this condition and the recognition of the heterogeneous clinical presentations. This will promote a lower threshold for testing for celiac disease in appropriate patients in the Middle East, using TTG antibody test which are relatively cheap, easily available, and very reliable with high sensitivity<sup>34</sup>.

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