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**Prevalence of Celiac Disease in Omani Adults with Iron Deficiency Anemia of
Unknown Cause**
A case-finding study

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Abstract

Objectives: This study aimed to estimate the serological prevalence of celiac disease in patients with IDA of unknown cause at primary health care facility. **Methods:** This is a prospective case finding study that was conducted at the primary care clinics in the Sultan Qaboos University Hospital (SQUH) from September 2018 to June 2020. A total of 104 patients aged 18 to 55 years old, with a hemoglobin (Hb) level less than 11.5 g/dl for males and less than 11.0 g/dl for females and a ferritin level less than 30 ng/mL for males and less than 13 ng/mL for females participated in the study. Blood samples were obtained for an initial serological screen using serum IgA level and then those with normal level of IgA, had IgA- Anti-tissue transglutaminase antibody (tTG) and IgA- anti-deamidated gliadin peptide (DGP). Positive IgA-tTG test was confirmed using IgA-endomysial antibodies. Patients with low IgA level were tested using IgG-

tTG and IgG-DGP. **Results:** Eight patients out of the 104 (7.7%) found to have positive serological screening for celiac disease. Three patients out of the eight (37.5%) had a positive IgA tTG. Two of those three (66.7%) had a positive IgA-endomysial antibody as well. The IgA-DGP was positive in seven patients out of the 104 (6.7 %). Out of those seven patients, two also had a positive IgA tTG. **Conclusion:** Celiac disease is not a rare disorder. There is a need to increase awareness among healthcare professionals about celiac disease and its non-classical manifestations such as IDA.

Keywords: cervical smears, conventional slides, ThinPrep slides, cervical organisms.

Advances in Knowledge

- This study is the first to report the prevalence of celiac disease serology in Omani adults with iron deficiency anemia (IDA) of unknown cause presenting to primary health care.

Application to Patient Care

- Celiac disease is not a rare disorder and it should be considered in patients with anemia especially when there is a positive family history of the disease. This can be done easily by assessment of IgA level followed by a combination of tests (tTGA and EMA) and DGP based on the IgA deficiency status.
- The findings of this study stresses on the increased need to upsurge awareness among healthcare professionals about celiac disease and its non-classical manifestations such as IDA. Our findings will encourage the development of guidelines for the investigation of celiac disease in general and in patients with unexplained IDA specifically. These measures will not only benefit the patient, but will significantly improve the healthcare system.

Introduction

Celiac disease (CD) is a chronic autoimmune disorder of the small bowel that is triggered by exposure to dietary gluten. The dietary sources of gluten include wheat, rye, barley and possibly oats.¹ CD causes chronic mucosal inflammation, villous atrophy, and crypt hyperplasia.² The main treatment is a lifelong commitment to gluten free diet.

Multiple serological approaches have been described to help in the diagnosis of celiac disease. This includes assessment of IgA-endomysial antibody (EMA), IgA-tissue transglutaminase antibody (tTG), and IgA-deamidated gliadin peptide antibody (DGA).³ In general, studies have shown that serum IgA-EMA and IgA-tTG testing have the highest diagnostic accuracy with a sensitivity of 95% and a specificity close to 100%.² However, there are variations reported between different laboratories.⁴ The newer anti-deamidated gliadin peptide (DGP) assays display higher diagnostic accuracy as compared to the older anti-gliadin antibody.⁵ Moreover, IgA deficiency is commonly seen in patients with celiac disease. Therefore, IgG against tTG and DGP are employed in testing for celiac disease in such patients. In addition, genetic testing for human leukocyte antigen HLA-DQ2 and HLA-DQ8 have been used to help in resolving cases with high clinical suspicion with doubtful or discrepant serology or histology.³ For a definitive diagnosis, upper esophagogastroduodenoscopy with a small bowel biopsy should be performed for any patient with positive serology or a high probability of having the disease (>5 percent), regardless of the serology results.⁶

The clinical manifestations of celiac disease depend on the age of the patient.⁷ In the pediatric age group, common intestinal manifestations include diarrhea, abdominal pain, distension, loss of appetite, weight loss and failure to thrive. However, later in life, many patients present with subtle symptoms including irritable bowel syndrome (IBS)-like presentation with alternating bowel habit, nausea and vomiting.

Up to 60% and 62 % of the pediatric and adult patients respectively present with extra intestinal manifestations.⁸ Examples of such presentation range from poor growth, anemia, elevated liver enzymes, arthralgia, and decreased bone mineral density and dermatitis herpetiformis.⁹ Similar to the intestinal manifestations, presence of some of those manifestations depends on the age. Poor growth is pure a pediatric presentation, whereas osteoporosis and dermatitis herpetiformis are adult manifestations.^{10, 11}

The mass screening for celiac disease in the general population in four European populations reported in 2010 revealed a prevalence of 1%.¹² On the other hand, information about prevalence of celiac disease among the Arab populations is sparse and based on small-scale studies.¹³ A

recent study in Saudi Arabia reported a prevalence of positive celiac disease serology of 1.5% among adult blood donors.¹⁴

Anemia is a unique presentation of CD. Up to 40 % of patients can present with anemia.¹¹ Conversely a good proportion of patients with CD present only with IDA. At the level of tertiary care, the prevalence of CD among patients presenting to hematology clinic with IDA was found to be 14.6%, 4% among Caucasian and 0% among non-Caucasian.¹⁵⁻¹⁶ In contrast the prevalence of CD among Iranian and Indian patients presenting with IDA was found to be 10.4% and 11% respectively.¹⁷⁻¹⁸ In Oman, the frequency was found to be 4% among patients with IDA presenting to the hematology clinic at a tertiary care facility.¹⁹

Primary health care workers often fail to test for CD in patients presenting with extra intestinal manifestations such as IDA leading to delay in the diagnosis in western countries.²⁰⁻²¹ It is expected to be the same in the Middle East and Arab countries. Therefore, this study aimed mainly to estimate the prevalence of celiac disease among Omani adults with IDA of unknown cause, attending the primary care facility at the Sultan Qaboos University Hospital (SQUH).

Methods

A prospective case finding study was conducted at the students' and the family medicine clinics in SQUH from September 2018 to June 2020. These two clinics are both under the Department of Family Medicine and Public Health, and provide primary care services to all Sultan Qaboos University (SQU) students and staff working in SQU and SQUH, and their families who come from all over Oman, and so the sample is representative of the whole country.

The hospital health information system (HIS) was searched for all patients with IDA attending both clinics over the past four years from 2016 to 2019. The target population for this study was all Omani adults, aged 18 to 55 years old, with a hemoglobin (Hb) level less than 11.5 g/dl for males and less than 11.0 g/dl for females and a ferritin level less than 30 ng/mL for males and less than 13 ng/mL for females (according to the local laboratory reference ranges). Patients with a known cause of IDA were excluded from the study, that is history of hematemesis, melena, menorrhagia, frequent blood donation, post-bariatric surgery, pregnant women or two months

post-partum, and lactating women. A total of 451 patients were identified through the HIS to have IDA and 282 patients met the inclusion criteria. Only 104 patients agreed to participate in the study. All the participants were given general information about the research project including the proposed blood test, the targeted disease, and the possible outcome and treatment. A written informed consent with a statement of confidentiality was taken from all the participants and their privacy was maintained throughout. The study was anonymous, confidentiality was assured and emphasized, and all participants were given a study number, which was used for data analysis. They were all informed that their participation was voluntary and they had the right to withdraw from the study at any time.

Information was gathered on the participants' socio-demographics details including age, gender, past medical and surgical history, medication history, and smoking and alcohol consumption history. Further information comprised hemoglobin level (Hb), ferritin level, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), and red cell distribution width (RDW). Blood samples were sent for an initial serological screen tests using total level of IgA on SPA plus machine (Binding Site Group, UK). Those with normal level of total IgA, had IgA-tTG and IgA-DGP assessed by EUROIMMUN Analyzer I (Euroimmun, Germany). Positive test of IgA-tTG was confirmed using IgA-endomysial antibodies (Euroimmun, Germany). Patients with low IgA level were tested using IgG-tTG and IgG-DGP (Euroimmun, Germany). Confirmed cases were then offered a follow up appointment with their own treating doctors and a referral for further investigation with the gastroenterologist at the SQUH. Those who refused referral were offered an appointment with the dietician to start a gluten free diet.

The data statistical analyses were conducted using IBM SPSS statistic version 23 (IBM Corp. Released 2015. IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp). Descriptive statistics were used to describe the sample's characteristics and frequencies and percentages were reported for categorical variables.

The study was approved by the medical research ethic committee of the College of Medicine and Health Sciences, Sultan Qaboos University (SQU), Sultanate of Oman in 2018.

Results

A total of 451 patients were identified with iron deficiency anemia over the four-year period from 2016 to 2019 where 282 patients were eligible for the study; from which 104 patients agreed to participate in the study. All of the consented participants were female and their ages ranged from 18 to 48 years, with a mean age of 28.2 ± 8.4 years. All of the participants were nonsmokers and not alcohol consumers.

The mean Hb was 10.6 ± 0.7 g/dL (range: 8.2-10.9), ferritin 9.2 ± 3.5 μ g/L (range: 1.0-13.0), MCV 71.4 ± 6.6 fl (range: 57.6-100), MCH 22.2 ± 2.4 pg (range: 16.9-31.5) and RDW $15.8 \pm 2.5 \times 10^{12}$ /L (range: 11.8-22.5).

The IgA level was normal (median of 2.4 IU/L, reference range xx-xx) in the vast majority of the participants (n=103; 99.04%) and only one patient (0.96%) had a low level of IgA (<0.02 IU/L). Out of those with normal IgA, few (n=8; 7.8%) had a positive screening test for celiac disease. The mean age of these eight patients was 28.0 ± 8.6 years, the mean Hb was 10.9 ± 0.0 g/dL and ferritin 7.4 ± 4.6 μ g/L, MCV 77.7 ± 5.8 fl, MCH 24.4 ± 2.5 pg, and RDW $15.15 \pm 2.0 \times 10^{12}$ /L.

Three patients from the 8 patients (37.5%) had a positive IgA tTG with a mean concentration of 84.5 IU/L and median of 140 (reference range 0-20 IU/L). IgA-endomyisal antibodies was positive in two out of three patients (66.7%). The IgA-DGP was positive in seven patients (87.5%), with a mean concentration of 44.7 IU/L and median of 113.5 (reference range of 0-25 IU/L). Out of these seven patients, two also had a positive IgA tTG. (Figure 1)

Discussion

The current study is the first to report 7.8% prevalence of celiac disease serology in Omani adults with IDA of unknown cause presenting to primary health care. Hin H et al, reported in his study in the UK that the commonest mode of presentation of celiac disease was anemia with varying degree of severity. He recommended that celiac disease should be considered in patients with anemia especially when there is a positive family history of the disease.²² This can be done easily by assessment of IgA level followed by a combination of the highly sensitive and specific tests (tTGA and EMA) and DGP based on the IgA deficiency status.²³ Few studies have been

conducted in the Middle East using celiac disease associated antibodies including the combination of anti-tTGA and EMA for screening.²⁴

Pelkowski TD et al, reported that IDA refractory to oral supplementation was strongly associated with celiac disease where 10% of the study population had celiac disease which is comparable to our study.²³ In a study done in UK, it was found that approximately one in 30 patients with IDA and 1 in 200-300 of the general population had CD.^{14, 25} A study on SQU students showed that anemia is common in Oman where 40% of them had IDA. It was noted that 21% of those with IDA who agreed to be treated with oral iron therapy for three months, failed to respond to treatment.²⁶ This would suggest that these patients warrant screening for celiac disease.

Though classically, affected individuals with celiac disease have intestinal symptoms such as malabsorption and diarrhea, in the last few years occult forms of the disease presenting with non-specific extra-intestinal symptoms such as fatigue and isolated IDA have been recognized.^{22,}²⁷ The continuing use of rice as the major dietary carbohydrate in Oman would explain the lack of overt disease in adults but increasing imports of wheat containing foods might change all of this as it seems to be the case in Jordan.²⁸

There are multiple community characteristics, genetic, and environmental factors that affect the prevalence of celiac disease.²⁹ One of the most important factors that increases the risk of developing celiac disease is the genetic factor, especially human leukocyte antigen (HLA).³⁰ A familial aggregation is found in 5%–15% of patients with celiac disease.³¹ Consanguinity is very common in Oman with a high rate of more than 50%. In total, 39% of Omanis are married to their first cousins; Oman ranks among the top seven Arab countries in terms of consanguinity rates.^{32, 33} Consanguineous marriages can result in increased expression of rare genetic disorders. Another factor that may contribute to the increased prevalence is the change in dietary habits; the younger generation tends to consume more gluten-containing foods compared to the older generation who depend mainly on rice. In the literature, multiple environmental factors other than gluten are under research as possible contributing factor that causes loss of gluten tolerance such as early infant feeding, the spectrum of intestinal microorganisms and how they change over time, intestinal infections, and stressors in general.³⁴

In our study, all the participants were females. There were two male patients meeting the inclusion criteria, but they declined to participate in the study. A study done by Jansson-Knodell et al revealed that anemia was more common in women, but not at a statistically significant level, where approximately 37% of women and 25% of men had anemia.³⁵ The predominance of women in our study meeting the inclusion criteria is surprising. It may be due to the observed fact that in the student clinic, female students are more likely to seek medical attention than males, or it may reflect differences in diet and nutrition between men and women in the study population.

Multiple factors contribute to the under-recognition of celiac disease in general and in patients with IDA especially in the primary care setting. First and foremost, is the health care professionals' unawareness of the non-classical manifestations of celiac disease. Another reason is the lack of continuity of care in our primary care settings. To overcome this, we need to disseminate this information to the concerned physicians through regular CMEs, updates and conferences. Establishing well-structured services based on continuous and comprehensive follow up will also be helpful.

Our study has some limitations namely the small sample size compared to the statistical calculations. However, since the encounter studied is rare, it is acceptable as a starting point. The study reported prevalence of celiac disease among at risk subjects with IDA. Investigation for celiac disease among healthy subjects and others at risk, such as patients with osteoporosis is recommended. It would be helpful to study genetic predisposition by sending HLA DQ2, DQ8, or both. Moreover, it will pave the way for larger prevalence studies in the general population. Additionally, all the participants were female patients and the study was conducted in only one institution and the results may not be generalized to other regions of the country. A large-scale community-based study which includes all Omani governorates and various age groups and both genders would overcome some of these limitations.

Conclusion

Celiac disease is not a rare disorder as we previously thought. There is a need to increase

awareness among healthcare professionals about celiac disease and its non-classical manifestations such as IDA. Our findings will enable the development of guidelines and protocols for the routine investigation of celiac disease in general and in patients with unexplained IDA specifically. These measures will not only benefit the patient, but will significantly improve the healthcare system.

Conflict of interest

The authors declare no conflict of interest.

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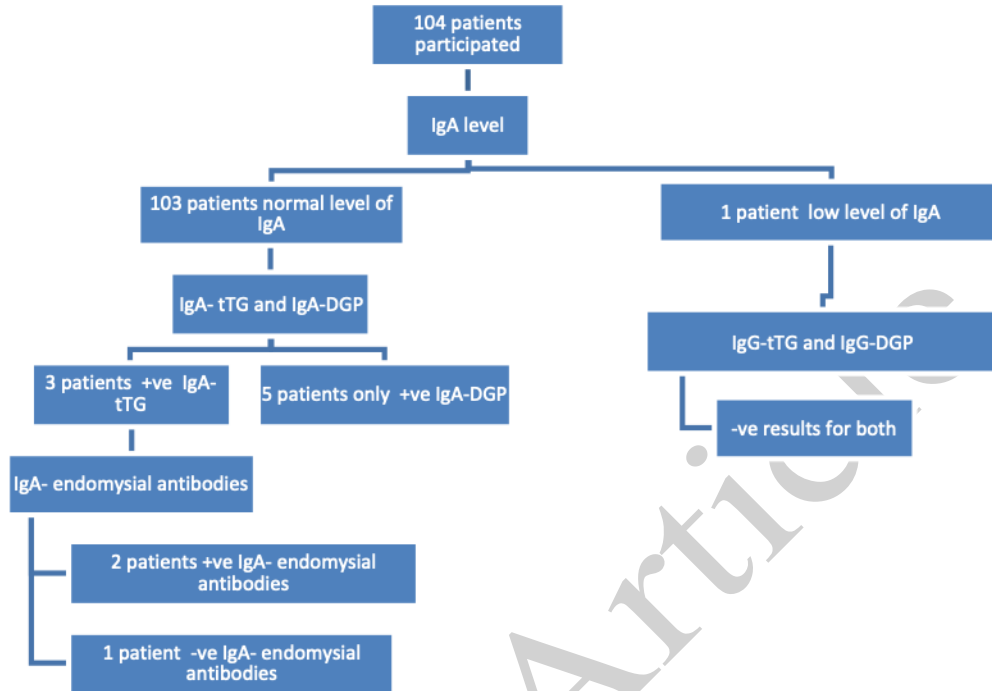


Figure 1: Flowchart for results of the serologic tests proven celiac disease. +ve: positive, -ve: negative; IgA-tTGA: anti-tissue transglutaminase IgA; IgA-DGP: anti-deamidated gliadin peptide IGA; IgG-tTG: anti-tissue transglutaminase IgG; IgG-DGP: anti-deamidated gliadin peptide IgG