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CLINICAL & BASIC RESEARCH

Prevalence of Coeliac Disease in Omani Adults with Iron Deficiency Anaemia of Unknown Cause

Case-finding study

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abstract: ***Objectives:*** This study aimed to estimate the serological prevalence of coeliac disease in patients with iron deficiency anaemia (IDA) of unknown cause at a primary healthcare facility in Oman. ***Methods:*** This prospective case-finding study was conducted at the primary care clinics in Sultan Qaboos University Hospital, Muscat, Oman from September 2018 to June 2020. Patients aged 18 to 55 years, with a haemoglobin (Hb) level <11.5 g/dL for males and <11.0 g/dL for females and a ferritin level <30 ng/mL for males and <13 ng/mL for females, were included in the study. Blood samples were obtained for initial serological screening using serum immunoglobulin (Ig)A level; those samples with normal levels of IgA, IgA anti-tissue transglutaminase antibody (tTG) and IgA anti-deamidated gliadin peptide (DGP) were determined. Positive IgA-tTG test was confirmed using IgA-endomysial antibodies. Patients with low IgA levels were tested using IgG-tTG and IgG-DGP. ***Results:*** A total of 104 patients participated in this study. Eight patients (7.7%) were found to have a positive serological screening result for coeliac disease; of these patients, three (37.5%) had a positive IgA-tTG result. Two of those three (66.7%) had a positive IgA-endomysial antibody. The IgA-DGP result was positive in seven (6.7%) of the 104 patients. Out of those seven patients, two also had a positive IgA tTG. ***Conclusion:*** Coeliac disease is not a rare disorder. There is a need to increase awareness among healthcare professionals about coeliac disease and its non-classical manifestations such as IDA.

Keywords: Celiac Disease; Iron-Deficiency Anemia; Serological Testing; Tissue Transglutaminase Antibody; Deamidated Gliadin Peptide; Oman.

Advances in Knowledge

- *This study is the first to report the prevalence of coeliac disease (CD) serology in Omani adults with iron deficiency anaemia (IDA) of unknown cause presenting to primary healthcare.*

Application in Patient Care

- *CD is not a rare disorder and should be considered a possibility in patients with anaemia, especially when there is a positive family history of the disease. This can be diagnosed easily by an assessment of the patient's immunoglobulin (Ig)A level followed by a combination of anti-tissue transglutaminase antibody and endomysial antibody tests and anti-deamidated gliadin peptide tests based on the IgA deficiency status.*
- *The findings of this study highlight the growing need to increase awareness among healthcare professionals about CD and its non-classical manifestations such as IDA. The findings encourage the development of guidelines for the investigation of CD in general and in patients with unexplained IDA specifically. These measures will not only benefit patients with CD but also significantly improve the healthcare system overall.*

Coeliac 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 intervention for CD is a lifelong commitment to a gluten-free diet.

Multiple serological approaches have been described to help in the diagnosis of CD, including assessments of the immunoglobulin A (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 offer the highest diagnostic accuracy levels, 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 than the older anti-gliadin antibody assays.[5] Moreover, IgA deficiency is commonly seen in patients with CD. Therefore, a test of IgG against tTG and DGP is employed for CD screening in at-risk patients. In addition, genetic testing for the human leukocyte antigens human leukocyte antigen (HLA)-DQ2 and HLA-DQ8 can help resolve cases with high clinical suspicion but doubtful or discrepant serology or histology.[3] For a definitive

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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%), regardless of the serology results.[6]

The clinical manifestations of CD depend on the age of the patient.[7] In the paediatric age group, common intestinal manifestations include diarrhoea, 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 habits, nausea and vomiting.

Up to 60% and 62% of paediatric and adult patients, respectively, present with extra-intestinal manifestations.[8] Examples of such presentations include poor growth, anaemia, elevated liver enzymes, arthralgia, decreased bone mineral density and dermatitis herpetiformis.[9] Similar to intestinal manifestations, the presence of some of these manifestations depends on age. For instance, poor growth is purely a paediatric presentation, whereas osteoporosis and dermatitis herpetiformis are adult manifestations.[10,11]

Mass screening for CD in four general European populations revealed a prevalence of 1% in 2010.[12] On the other hand, information about the prevalence of CD among Arab populations is sparse and based on small-scale studies.[13] A recent study in Saudi Arabia reported a prevalence of positive CD serology of 1.5% among adult blood donors.[14]

Anaemia is a unique presentation of CD. Up to 40% of patients with CD can present with anaemia.[11] Conversely, a good proportion of patients with CD present only with iron deficiency anaemia (IDA). At the tertiary level of care, the prevalence of CD among patients presenting with IDA at a haematology clinic was found to be 14.6%, with 4% prevalence among Caucasian patients and 0% among non-Caucasians.[15,16] More specifically, 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 at the haematology clinic of a tertiary care facility.[19]

Primary healthcare workers in Western countries often fail to test for CD in patients presenting with extra-intestinal manifestations such as IDA, leading to diagnostic delays.[20,21] The same scenario is expected to be present in Middle Eastern and Arab countries. Therefore, this study aimed to estimate the prevalence of CD among Omani adults with IDA of unknown cause.

Methods

A prospective case-finding study was conducted at the students' and family medicine clinics in Sultan Qaboos University Hospital (SQUH) from September 2018 to June 2020. These two clinics are both under the Department of Family Medicine and Public Health; they provide primary care services to all Sultan Qaboos University (SQU) students and staff, as well as their families from all over Oman. Therefore, the sample included patients from different regions of the country.

The hospital health information system (HIS) was searched for data on all patients with IDA at both clinics for the four-year period from 2016 to 2019. The target population for this study comprised Omani adults aged 18–55 years with a haemoglobin (Hb) level <11.5 g/dL for males and <11.0 g/dL for females and a ferritin level <30 ng/mL for males and <13 ng/mL for females (according to the local laboratory reference ranges). Patients with a known cause of IDA (i.e. a history of haematemesis, melena, menorrhagia, frequent blood donation or post-bariatric surgery) or women who were pregnant, two months post-partum or lactating were excluded from the study. A total of 451 patients were identified through the HIS to have IDA of which 282 patients met the inclusion criteria. Of these, 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 outcomes and treatment options. The study was anonymous, confidentiality was assured and emphasised and all participants were given a study number, which was used for data analysis.

The participants' socio-demographic details, including age, gender, past medical and surgical history, medication history and smoking and alcohol consumption history, were gathered. Further information on Hb level, ferritin level, mean corpuscular volume (MCV), mean corpuscular haemoglobin (MCH) and red cell distribution width (RDW) was also obtained for each patient. Blood samples were sent for initial serological screening tests using the total level of IgA on an SPA plus machine (Binding Site Group, UK). If total IgA was normal, IgA-tTG and IgA-DGP were assessed using the EUROIMMUN Analyzer I (Euroimmun, Germany). Positive test of IgA-tTG was confirmed using IgA-endomysial antibodies (Euroimmun). Patients with low IgA level were tested using IgG-tTG and IgG-DGP (Euroimmun). Confirmed patients were then offered follow-up appointments with their respective

treating doctors and a referral for further investigation with the gastroenterologist at the SQUH. Those who refused the referral were offered an appointment with the dietician to start a gluten-free diet.

The statistical analyses were conducted using the Statistical Package for the Social Sciences (SPSS), Version 23.0 (IBM SPSS Inc., Chicago, IL, USA). Descriptive statistics were used to describe the sample's characteristics and frequencies; percentages were reported for categorical variables.

The study was approved by the medical research ethics committee of the College of Medicine and Health Sciences, SQU, Oman in 2018 (#SQU-EC/221/18). Written informed consent with a statement of confidentiality was obtained from each participant and their privacy was maintained throughout the study. The patients were all informed that their participation was voluntary and that they had the right to withdraw from the study at any time.

Results

A total of 451 patients with IDA were identified over the four-year period from 2016 to 2019; 282 patients were eligible for the study, of which 104 patients agreed to participate in the study. All of the participants who consented were female and their ages ranged from 18 to 48 years (mean age: 28.2 ± 8.4 years). None of the participants drank alcohol or smoked.

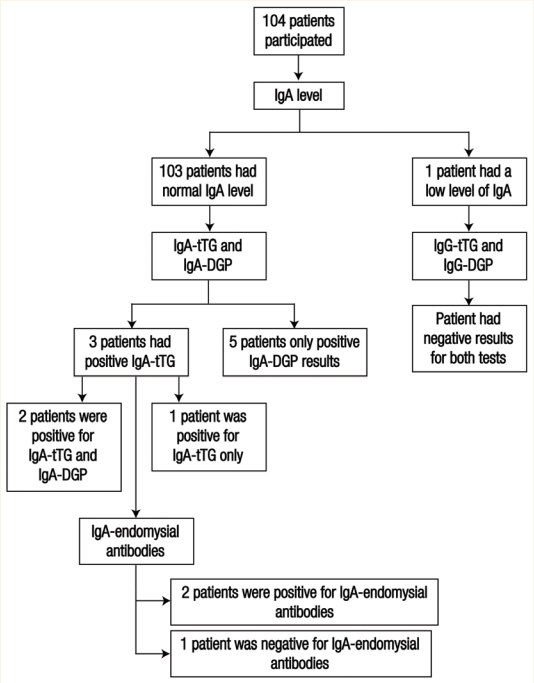

Figure 1: Flowchart showing the results of the serologic tests for coeliac disease in adult Omani patients

Ig = immunoglobulin; tTG = anti-tissue transglutaminase; DGP = anti-deamidated gliadin peptide.

The mean Hb level was 10.6 ± 0.7 g/dL (range: 8.2–10.9), ferritin level was 9.2 ± 3.5 µg/L (range: 1.0–13.0), MCV level was 71.4 ± 6.6 fL (range: 57.6–100 fL), MCH level was 22.2 ± 2.4 pg (range: 16.9–31.5 pg) and RDW was 15.8 ± 2.5 × 1012/L (range: 11.8–22.5 × 1012/L).

IgA levels were normal (median = 2.4 g/L, reference range: 0.85-4.9 g/L) in the vast majority of the participants (n = 103; 99.0%) and only one patient (1.0%) had a low level of IgA (<0.02 g/L). Out of those with normal IgA, eight patients (7.8%) were positively screened for CD. The mean age of these eight patients was 28.0 ± 8.6 years, mean Hb was 10.9 ± 0.0 g/dL, ferritin was 7.4 ± 4.6 µg/L, MCV was 77.7 ± 5.8 fL, MCH was 24.4 ± 2.5 pg and RDW was 15.15 ± 2.0 ×1012/L.

Three of the eight patients (37.5%) had positive IgA-tTG results with a mean concentration of 84.5 IU/L and median of 140 (reference range: 0–20 IU/L). Two out of these three patients (66.7%) tested positive for IgA-endomysial antibodies. 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: 0–25 IU/L). Of these seven patients, two also had a positive IgA-tTG [Figure 1].

Discussion

The current study is the first to report a 7.8% prevalence of CD serology in Omani adults with IDA of unknown cause at a primary healthcare centre. A study in the UK previously reported that the most common mode of presentation of CD is anaemia with varying degrees of severity and recommended that CD should be considered in patients with anaemia, especially when there is a positive family history of the disease.[22] CD can be easily screened by assessing the patient's IgA level, followed by a combination of the highly sensitive and specific tTGA and EMA tests and DGP based on the IgA deficiency status.[23] Few studies have been conducted in the Middle East using CD-associated antibodies and the combination of anti-tTGA and EMA for screening.[24]

Pelkowski and Viera reported that IDA refractory to oral supplementation was strongly associated with CD; 10% of the study population had CD, which is comparable to the present study.[23] Furthermore, a study conducted in the UK 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 students at SQU showed that anaemia is common in Oman, as 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 suggests that such patients should be screened for CD.

Although individuals with CD typically present with intestinal symptoms such as malabsorption and diarrhoea, occult forms of the disease with non-specific extra-intestinal symptoms, such as fatigue and isolated IDA, have been recognised in the last few years.[22,27] The continuing use of rice as the primary source of dietary carbohydrates in Oman explains the lack of overt disease in adults, but this may change with the increasing import of wheat-containing foods, as is the case in Jordan.[28]

There are multiple community characteristics as well as genetic and environmental factors that affect the prevalence of CD.[29] Genetic factors can significantly increase the risk of developing CD, especially the presence of the HLA.[30] A familial aggregation is found in 5–15% of patients with CD.[31] Consanguinity is very common in Oman at a 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 an increased expression of rare genetic disorders. Changes in dietary habits constitute another factor that may contribute to the increased prevalence of CD; the younger generation tends to consume more gluten-containing foods than the older generation that depends mainly on rice. In the literature, multiple environmental factors other than gluten have been researched as possible contributing factors that reduce gluten tolerance; these include early infant feeding, the spectrum of intestinal microorganisms and how they change over time, intestinal infections and stressors in general.[34]

In the present study, all the participants were female. Two male patients met the inclusion criteria, but they declined to participate in the study. A study by Jansson-Knodell *et al.* revealed that anaemia is more common among women but not at a statistically significant level; approximately 37% of the women and 25% of the men in their study had anaemia.[35] The predominance of women in the present study was surprising. It may be because female students are more likely to seek medical attention at the clinic than male students or this may reflect differences in diet and nutrition between men and women in the study population.

Multiple factors contribute to the under-recognition of CD in general and in patients with IDA in particular, especially in the primary care setting. The first and foremost cause is the lack of awareness among healthcare professionals about the non-classical manifestations of CD. Another reason is the lack of continuity of care in primary care settings. To overcome this gap in healthcare, it is necessary to disseminate relevant information to the concerned physicians through regular continuing medical education, updates and conferences. Establishing well-structured services based on continuous and comprehensive follow-ups would also be helpful.

There are some limitations to the present study, namely the small sample size used for the statistical calculations. However, this is acceptable as a starting point since research on this condition from the Middle East is rare. The study reported the prevalence of CD among at-risk subjects with IDA. Investigation of CD among healthy subjects and others at risk, such as patients with osteoporosis, is recommended in the future. It would be helpful to study genetic predisposition to CD by considering HLA-DQ2 or HLA-DQ8 or both. This can pave the way for larger prevalence studies in the general population. Additionally, all the participants in the present study were female patients and the study was conducted at a single institution with a small sample size; therefore, the results may not be generalised to other regions of the country. A large-scale community-based study that includes all Omani governorates, various age groups and both genders would overcome some of these limitations.

Conclusion

CD is not a rare disorder as it was previously thought to be. There is a need to increase awareness among healthcare professionals about CD and its non-classical manifestations such as IDA. The present study's findings enable the development of guidelines and protocols for the routine investigation of CD in general and in patients with unexplained IDA specifically. These measures will not only benefit CD patients but also significantly improve the healthcare system overall.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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AUTHORS' CONTRIBUTION

SA, AMB, AS, RD and RK conceived the research idea and performed the literature review. SA and AMB—under the supervision of RD, AS and RK—designed

the research methodology and the data collection sheet. SA, AMB, JA and MK were involved in the data collection and date entry. SA, AMB, AS, JA, MK and RK analysed and interpreted the results. SA, AMB, AS and RK had a major contribution in drafting the manuscript in consultation with RD, JA and MK. RK was the research supervisor who guided SA and AMB throughout the project. All authors read and approved the final version of the manuscript.

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