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Assessment of Iron Status in Iraqi Females at Reproductive Age Affected with Celiac Disease

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Abstract

Celiac disease (CD) is a serious autoimmune disease that occurs in people who eat gluten, leading to damage to the small intestine and nutrients that cannot be properly absorbed into the body. The study population consists of 140 female participants, 100 of whom have CD at reproductive age and are matched with apparently healthy females of the same age. The study was carried out in the Chemistry Department at the University of Baghdad and Baghdad Educational Hospital (Baghdad, Iraq). The present study aimed to evaluate the effect of CD on iron indices in females who have anemia and others who do not. Iron, unsaturated iron-binding capacity (UIBC), Total iron binding capacity (TIBC), ferritin, transferrin, and Complete blood count (CBC) were measured. According to the study findings, 28(28%) of the female patients had Hb equal to or greater than 12, while 72(72%) of them had Hb less than 12. Hematological indices also revealed numerous significant differences ($P<0.05$) between the patient and control groups. The iron indicators of the patients were measured and revealed significant variations that indicated the presence of iron deficiency anemia. Iron, ferritin, and Transferrin were decreased in patients compared to the control group, while TIBC, UIBC, and transferrin were increased. This study demonstrated that the majority of newly diagnosed female CD participants had Hb levels less than 12, as well as low iron and ferritin levels. Hematological indices also indicated iron deficiency anemia.

Keywords: Celiac disease, IDA, Ferritin, Hematology indices

تقييم حالة الحديد لدى الإناث العراقيات في سن الإنجاب المصابات بمرض الاضطرابات الهضمية

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الخلاصة

مرض الاضطرابات الهضمية هو أحد أمراض المناعة الذاتية الخطيرة التي تحدث عند الأشخاص الذين يتناولون الغلونين و يؤدي إلى تلف الأمعاء الدقيقة و لا يمكن امتصاص العناصر الغذائية بشكل صحيح في الجسم. تم إجراء مجموعة الدراسة في قسم الكيمياء في جامعة بغداد ومستشفى بغداد التعليمي (بغداد، العراق)، مع 100 مشاركة من الاضطرابات الهضمية في سن الإنجاب مع 40 أنثى سليمة من نفس العمر. هدفت الدراسة الحالية إلى تقييم تأثير مرض الاضطرابات الهضمية على مؤشرات الحديد لدى الإناث المصابات بفقر الدم و غيرهن من غير المصابات به. تم قياس الحديد و قدرة ربط الحديد و الحديد غير المشبع و سعة ربط

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الحديد الكلية و الفيريتين و الترانسفرين و تعداد الدم الكامل وفقًا لنتائج الدراسة، كان لدى 28 (28٪) من المريضات نسبة هيموكلوبين تساوي أو تزيد عن 12 ، بينما كان لدى 72 (72٪) منهن أقل من 12. كشفت المؤشرات الدموية أيضًا عن اختلافات معنوية عديدة (<0.05) بين مجموعة المريضات ومجموعة الأصحاء. تم قياس مؤشرات الحديد لدى المريضات و كشفت عن وجود اختلافات معنوية تشير إلى وجود فقر الدم الناجم عن نقص الحديد. انخفض الحديد، الفيريتين، و الترانسفيرين في المرضى مقارنة بمجموعة التحكم، بينما تمت زيادة قدرة ربط الحديد و الحديد غير المشبع و سعة ربط الحديد الكلية، و الترانسفيرين. أظهرت هذه الدراسة أن غالبية النساء اللواتي تم تشخيصهن حديثًا بمرض الإضطرابات الهضمية كان لديهن مستويات الهيموغلوبين أقل من 12، بالإضافة إلى مستويات منخفضة من الحديد و الفيريتين. كما أشارت مؤشرات الدم إلى فقر الدم بسبب نقص الحديد.

1. Introduction

Celiac disease (CD) is an immune-mediated gluten-dependent enteropathy that affects the small bowel and is an autoimmune condition characterized by a specific serological and histological profile triggered by gluten ingestion in genetically predisposed individuals [1,2-5]. Celiac sprue, another name for celiac disease [6], causes immune dysregulation and immune attacks on target tissues [7]. Gluten is a common, alcohol-soluble protein found in grains such as wheat, barley, rye, spelt, and kamut [3,8]. Celiac disease, also known as gluten-sensitive enteropathy, can cause symptomatic malabsorption and a variety of symptoms such as diarrhea, bloating, and fatigue. Celiac disease requires an appropriate diagnosis since untreated celiac disease can result in iron, vitamin D, and vitamin B12 deficiency, as well as intestinal cancer [3, 9]. The primary single environmental trigger is eating gluten (gliadin), which is required for disease development [10]. Despite the necessity for accurate identification, there is a significant overlap between celiac disease and other gastroenterological conditions such as irritable bowel syndrome, making celiac disease diagnosis difficult and time-consuming [11]. Celiac disease is diagnosed with serologic testing, often via tissue transglutaminase antibody (TTG-IgA), with or without a duodenal biopsy. If serologic testing is positive and there is a high pre-test probability for celiac disease, or if the serologic testing results are incompatible, a duodenal biopsy is usually performed, Immunologic factors are also important, with CD patients having high levels of Anti-Tissue Transglutaminase (Anti-TTG), Anti-Endomyseal (Anti-EMA), and Anti-Deaminated Gliadin (DGP) antibodies. IgA is another immunological variable that can be raised in CD patients, while IgM and IgG are less specific [12]. Females are affected by CD as much twice as males [13]. The only effective treatment is a strict, lifelong gluten-free diet (GFD) that excludes all gluten [14]. Anemia is one of the most prevalent clinical signs of CD, and it may be present in more than half of patients at the time of diagnosis [15,16]. Iron deficiency anemia (IDA) is frequently the only clinical symptom of CD in both children and adults, particularly in patients with subclinical or atypical CD [16]. Indeed, IDA is the most common type of anemia and one of the most prevalent human diseases, affecting nearly 20% of the world's population [17]. Up to 50% of females at reproductive age have an IDA prevalence [18]. Naturally, there is equilibrium between gaining and consuming iron, and ID occurs when this equilibrium becomes negative. Considering special growth conditions, ID is a major cause of anemia, despite the fact that there are several reasons for anemia [19]. Iron insufficiency in celiac disease is caused mostly by reduced iron absorption, but there may also be unexplained blood loss in the gastrointestinal (GI) tract. A GFD and iron supplements are the major treatments for IDA connected to CD until the iron stores are replenished. For the hemoglobin to return to normal and for the iron stores to be fully replenished, this process can take up to a year [20]. Iron is a strong pro-oxidant [21] involved in controlling how live cells differentiate and develop [22]. Fatigue and decreased oxygenation of the muscles are side effects of iron deficiency anemia, which may impact muscle strength and quality and,

ultimately, athletic performance [17]. Because of the aberrant immunological response brought on by celiac disease, the small intestine mucosa becomes chronically inflamed and eventually loses its intestinal villi [4], which reduces the absorption of numerous nutrients, including iron [15,23]. So, to assess iron status and IDA in Iraqi females at reproductive age affected with celiac disease, this goal was in the present study.

2. Material and method

This study included 141 participants, 100 of whom were Iraqi females recently diagnosed with celiac disease (P, age = 16-35 years), and 41 apparently healthy females who served as controls (C, age = 16-35 years). Following a thorough physical examination and a clinical history, tests such as hemoglobin, RBC indices, serum iron, total iron binding capacity, and serum ferritin were done. From September 2021 to January 2022, a study population was undertaken in the Department of Chemistry at Baghdad Educational Hospital (Baghdad, Iraq). All participants in this study were undergoing medical examinations at Baghdad Educational Hospital. Women who were postmenopausal, pregnant, or had other digestive issues or illnesses, or who used dietary iron supplements, were not included in the study. Other systemic problems, such as inflammatory bowel disease, intestinal parasites, irritable bowel syndrome, cystic fibrosis, and immunological diseases, were not considered in the study. Personal interviews with a series of pre-made questionnaires were used to collect all the data.

3. Biochemical and hematology

The Roche company kit is used to determine serum Iron and serum UIBC by a fully automated colorimetric method. The results are expressed in terms of micrograms per deciliter. Total iron binding capacity was calculated from the following equation [23]:
TIBC = UIBC + Iron

Human transferrin is determined turbidimetrically by the Roche company kit. The results are expressed in terms of milligrams per deciliter. The percentage of Transferrin saturation was calculated from the following equation [23]:
Transferrin saturation (%) = (Serum Iron x 100) / TIBC.

The Roche company kit is used to determine serum ferritin by the electrochemiluminescence immunoassay "ECLIA". The results are expressed in nanograms per milliliter. Complete Blood Count (CBC) The blood was drawn, placed in an EDTA tube, and shaken kindly for 2 minutes; then the test began automatically when the needle of the apparatus took out the needed blood aliquots. The icon 3 apparatus by Norma Company (Hungary) was used. The data was analyzed using statistical tools (SPSS 26.0; IBM Inc., Chicago, IL, USA). The mean and standard deviation of variables with homogeneous distributions were calculated and compared using the one-way ANOVA test. P values less than 0.05 were used to define statistical significance.

3. Results and discussion

The present study includes 100 Iraqi females at reproductive age newly diagnosed with celiac disease (P), with 41 apparently healthy females serving as the control group (C). The range of ages was 16-35 for all the individuals who participated. Diarrhea and weight loss were the most prevalent signs at the time of presentation (64 patients); 36 patients were asymptomatic. The patients' group (P) was further divided into two groups: the G1 group, consisting of 28 patients with a hemoglobin level of 12 or more, and the G2 group, consisting of 72 patients with a hemoglobin level less than 12. The results obtained from the present study are listed in Table 1 which revealed that there was no significant difference in age between all the studied groups ($P>0.05$). BMI were significantly lower ($P=0.000$) in the G1 (18.35±1.38

Kg/m^2) and G2 (19.07±1.65 Kg/m^2**)** groups as compared to the C group (21.64±2.43 Kg/m^2), while there was no significant difference (P=0.202) between the G1 and G2 groups. In addition, Table 1 showed that anti-Ttg levels in G1 (13.70±6.94 IU/mL) and G2 (18.00±9.91 IU/mL) were significantly higher (P=0.000) as compared to the C group (2.73±0.70 IU/ml), while there was no significant difference (P=0.037) between the G1 and G2 groups. The levels of IgA in G1 (12.69±1.56 IU/mL) and G2 (16.45±11.02 IU/mL) were significantly higher (P=0.000) as compared to the C group (2.05±0.49 IU/mL), while there was no significant difference (P=0.094) between G1 and G2. There was no significant difference (P=0.485) between G1 (43.79±18.42 µg/dL) and G2 (39.32±15.91 µg/dL) in Iron levels, but G1 and G2 showed a lower significant difference (P=0.000) as compared to the C group (67.14±19.27 µg/dL). Ferritin levels showed a significant decrease in G1 (26.44±14.01 ng/mL) and G2 (25.26±13.74 ng/mL) as compared to the C group (52.14±12.20 ng/mL) (P=0.000), while there was no significant difference between G1 and G2 (P=0.917). The results of the present study showed that most of the newly diagnosed patients were anemic. Iron and ferritin levels were low in patients as compared to the C group (G2 has the lowest value); these results were identical to the results obtained by Daya *et al*. in 2013 [16], Farag AL-Mosawi in 2012 [24], and Kapur *et al*. in 2003 [25]. Another study found that ferritin levels were low in CD patients without anemia [25]. Serum ferritin, a stable glycoprotein, accurately indicates iron storage in the absence of inflammatory changes. It is being proven that ferritin is the first to go awry when iron levels run low, and it is unaffected by recently eaten iron. Despite being an acute-phase reactant, the ferritin test is often considered the best test for determining ID in patients with malabsorption [10]. The small intestine is harmed by CD, which prevents the correct absorption of nutrients from food. Damage to the upper two portions of the intestine, where vitamins B12 and iron are absorbed, occurs in the early stages of the disease. Later, damage develops to the lower portion of the intestine. Anemia is caused by inadequate absorption of iron, folate, or vitamin B12, which interferes with the generation of healthy red blood cells [26]. Iron deficiency anemia is a common health condition that affects many people around the world. Sometimes IDA is the only symptom of celiac disease. In spite of adequate oral iron intake, IDA in CD is caused by inadequate iron absorption from inflamed and damaged small intestine mucosa. When there is microcytic hemolytic anemia, low iron, and an increase in total iron binding capacity (TIBC), IDA is diagnosed [2].

Table 1: Mean value ± SD for studied parameters among different groups (n=141)

Parameters	Control Hb≥12,(C, n=41)	Patients with Hb≥12, (G1, n=28)	Patients with Hb <12, (G2, n=72)	Groups	P value
Age (Year)	25.00±5.80	25.10±2.76	25.04±5.18	C&G1	0.996
				C&G2	0.999
				G1&G2	0.998
BMI (Kg/m^2)	21.64±2.43	18.35±1.38	19.07±1.65	C&G1	0.000**
				C&G2	0.000**
				G1&G2	0.202
Anti-TtG (IU/mL)	2.73±0.70	13.70±6.94	18.00±9.91	C&G1	0.000**
				C&G2	0.000**
				G1&G2	0.037*
IgA (IU/mL)	2.05±0.49	12.69±1.56	16.45±11.02	C&G1	0.000**
				C&G2	0.000**
				G1&G2	0.094
Iron(µg/dL)	67.14±19.27	43.79±18.42	39.32±15.91	C&G1	0.000**

				C&G2	0.000**
				G1&G2	0.485
Ferritin (ng/mL)	52.14±12.20	26.44±14.01	25.26±13.74	C&G1	0.000**
				C&G2	0.000**
				G1&G2	0.917
TIBC (µg/dL)	329.47±52.80	355.27±53.77	373.36±69.71	C&G1	0.212
				C&G2	0.001**
				G1&G2	0.395
UIBC (µg/dL)	288.14±60.65	289.74±62.95	334.63±71.95	C&G1	0.995
				C&G2	0.002**
				G1&G2	0.009**
TRSF (mg/dL)	242.65±24.03	308.91±53.78	331.54±61.69	C&G1	0.000**
				C&G2	0.000**
				G1&G2	0.126
TRST (%)	20.82±6.07	19.45±9.70	10.74±5.35	C&G1	0.677
				C&G2	0.000**
				G1&G2	0.000**

*P<0.05; **P<0.001; no significant P>0.05.

The results in Table 1 also revealed no significant difference in TIBC between G1 and C groups (P=0.212) or between G1 (355.27±53.77 µg/dL) and G2 (373.36±69.71 µg/dL) (P=0.395) groups, while there was a significant difference between the G2 and C groups (329.47±52.80 µg/dL) (P=0.001). UIBC showed no significant difference between the G1 and C groups (P=0.995), while a significant difference (P=0.002) was found between the G2 and C groups and between the G1 (289.74±62.95 µg/dL) and G2 groups (334.63±71.95 µg/dL). Transferrin levels showed a significant increase (P=0.001) in the G1 (308.91±53.78 mg/dL) and G2 (331.54±61.69 mg/dL) groups as compared with the C group (242.65±24.03 mg/dL), while no significant differences (P=0.126) were found between the G1 and G2 groups. The levels of TIBC, UIBC, and transferrin were elevated in the two groups of patients included in the present study as compared to the healthy subjects. These results were similar to those results obtained in previous studies [24,25]. In another study, the level of TIBC was elevated in CD patients despite the absence of anemia [27]. The presence of iron binding sites on transferrin is indicated by the TIBC. In an iron shortage, values rise, while in an iron overload, values decrease [24]. Transferrin saturation (TRST) was significantly lower (P=0.000) in G2 (10.74±5.35 %) as compared to the G1 (19.45±9.70 %) and C (20.82±6.07%) groups. While there was no significant difference between the G1 and C groups (P=0.667). Transferrin is about 30% saturated with iron, and Iron deficiency anemia is indicated by transferrin saturation [6]. Transferrin saturation does not quantitatively represent iron reserves but rather increases in iron excess and decreases in iron deficiency [28]. This was confirmed by our results, which showed that the anemic patients had the lowest value of TRST compared to healthy subjects. The hematology parameters were measured for celiac and healthy females as listed in Table 2. The levels of Hb showed a significant decrease (P=0.000**)** in G2 (9.62±01.44 g/dc**)** as compared to the C (13.03±0.64 g/dc) group and also between G2 (9.62±01.44 g/dc) and G1 (12.85±0.74 g/dc) groups (P=0.000), while no significant variation was found between G1 and C groups. In a previous study on adults (males and females) with a mean age at the time of presentation of 26.15±13.3 years, the Hb levels were 8.9 ± 2.6 g/dL.

Table 2: Mean value ± SD for hematology parameters among different groups (n=141)

Parameters	Control Hb≥12,(C, n=41)	Patients with Hb≥12, (G1, n=28)	Patients with Hb <12, (G2, n=72)	Groups	P value
Hb (g/dc)	13.03±0.64	12.85±0.74	9.62±01.44	C&G1	0.795
				C&G2	0.000**
				G1&G2	0.000**
RBC (10^6/µL)	4.59±0.54	4.50±0.95	3.53±0.34	C&G1	0.787
				C&G2	0.000**
				G1&G2	0.000**
WBC (10^3/µL)	6.41±1.33	6.29±1.69	6.40±1.27	C&G1	0.934
				C&G2	0.999
				G1&G2	0.930
MCV (fL)	86.32±6.22	90.07±6.39	86.63±8.82	C&G1	0.120
				C&G2	0.976
				G1&G2	0.116
MCH (pg)	28.74±3.07	28.78±3.39	29.65±4.44	C&G1	0.999
				C&G2	0.462
				G1&G2	0.575
MCHC (g/dL)	32.28±1.35	31.62±2.30	32.00±2.74	C&G1	0.485
				C&G2	0.809
				G1&G2	0.751
LY (%)	34.70±8.24	32.14±6.85	35.10±7.38	C&G1	0.353
				C&G2	0.960
				G1&G2	0.187
MO (%)	4.65±1.74	5.63±1.42	6.35±1.70	C&G1	0.048*
				C&G2	0.000**
				G1&G2	0.126
GR (%)	60.84±8.11	63.41±6.03	61.37±6.68	C&G1	0.295
				C&G2	0.919
				G1&G2	0.394
RDWCV (%)	13.16±1.10	13.93±2.69	13.75±2.18	C&G1	0.280
				C&G2	0.315
				G1&G2	0.914
RDWSD (fL)	43.05±5.66	46.23±7.36	49.88±10.76	C&G1	0.093
				C&G2	0.001**
				G1&G2	0.090

*P<0.05; **P<0.001; no significant P>0.05.

The findings of the latter study are similar to the results obtained from the present study [29]. Another study revealed that adults (males and females) (age >18 years and <45) had Hb levels of 10.6±1.1 g/dL [30]. In addition, another study took place on women of reproductive age with IDA; the Hemoglobin level (g/dL) was 9.43 ±1.57.This study suggested possible causes of anemia, among which were auto-immune diseases [31]. The red blood cells (RBC) were

significantly decreased in G2 (3.53±0.34 $10^{\wedge 6}$/µL) as compared to the C group (4.59±0.54 10^6/µL), and in G2 (3.53±0.34 $10^{\wedge 6}$/µL) as compared with the G1 group (4.50±0.95 10^6/µL). No differences were found in RBC between the G1 and C groups. Monocyte (MO) levels were elevated in the two groups of patients, G1 (5.63±1.42%) and G2 (6.35±1.70%) as compared with the C group (4.65±1.74%). A significant increase (P=0.001) was found in RDWSD between G2 (49.88±10.76 fL) and C group (43.05±5.66 fL), while no significant variation between G1 and C groups or G1 and G2 groups. The degree of anisocytosis on the peripheral blood smear, as reflected by the red cell distribution width (RDW), is a measurement of RBC size variance. A low RDW indicates a homogeneous population of RBCs, whereas a high RDW indicates a wide range of RBC sizes. A high RDW can be seen in a variety of anemias, including ID, vitamin B12 or folate deficiency, myelodysplastic syndrome (MDS), hemoglobinopathies, and people with anemia who have had transfusions [10]. Table 1 indicates no significant differences (P>0.05) between other hematology factors as compared with the C group. The elevated levels of LY, GR, and MO indicate autoimmune disease; likewise, high TTG levels are associated with inflammation, autoimmune disease, and anemia [13,24].

4. Conclusion

It is concluded from the present study that most of the newly diagnosed female participants with CD had Hb levels less than 12, and they showed low iron and ferritin levels. Hematological indices also gave indications of iron deficiency anemia.

Ethics clearance

The research ethical committee at scientific research has the ethical approval of environmental, health, higher education, and scientific research ministries in Iraq

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