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**Vitamin D Status in Newly Diagnosed Celiac Disease Patients**

**Raghad H. Sanyi, Tuqa Sami Al-Salmani and Izzat A. Al-Rayahi**

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**Abstract**

Celiac disease is an inflammatory disorder involving the small bowel, in addition to other organs. An inappropriate immune response to dietary gluten mainly in genetically predisposed individuals lies behind the persistent inflammation of the mucosa lining the proximal small bowel. Malabsorption in celiac disease patients lead to deficiencies in a number of minerals and vitamins. Among the affected vitamins is vitamin D. The present study aimed to figure out the prevalence of vitamin D deficiency in celiac disease patients and investigate whether any vitamin D deficiency could associate with the level of autoantibodies. Forty-six early diagnosed celiac disease patients (11 males and 35 females) were consecutively recruited from Special Nursing Hospital \ Baghdad, during the period from July 2018 to February 2019. Twenty apparently healthy subjects were also recruited to serve as a control group. Age distribution of patients showed that 43.7% of patients were between 10 and 20 years old. On the other hand, 6 (13%), 1 (2.1%) and 4 (8.6%) patients were in the age groups 20-30, 30-40 and 40-50 years respectively. Female patients were more than male patients (66 and 34% respectively). Celiac disease patients had a significantly lower level of vitamin D in comparison with the control ( $14.3 \pm 9.9$  and  $68 \pm 4$  ng/ml respectively). In addition, 71.73% of celiac disease patients had vitamin D deficiency, 23.91% had vitamin D insufficiency, while 4.34% of celiac disease patients had vitamin D sufficiency. On the other hand, 100% of control subjects had vitamin D sufficiency. Nevertheless, no statistical difference in the level of vitamin D was found between

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female and male patients ( $15.3 \pm 10.08$  and  $12.58 \pm 8.9$  ng/ml respectively). It can be concluded that vitamin D is significantly decreased in patients with celiac disease.

**Keywords:** Gluten, celiac disease, vitamin D, inflammation.

**حالة فيتامين (د) في مرضى الداء البطني المشخصين حديثاً**

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**الخلاصة**

مرض الداء البطني هو اضطراب التهابي يصيب الأمعاء الدقيقة بالإضافة إلى الأعضاء الأخرى. تكمن الاستجابة المناعية غير المناسبة للغلوتين الغذائي بشكل رئيسي في الأفراد المهيئين وراثياً وراء الالتهاب المستمر في الغشاء المخاطي المبطن للأمعاء الدقيقة القريبة. يؤدي سوء الامتصاص لدى مرضى الداء البطني إلى نقص في عدد من المعادن والفيتامينات. من بين الفيتامينات المتأثرة هو فيتامين د. لذلك هدفت الدراسة الحالية إلى تحديد مدى انتشار نقص فيتامين د في مرضى الداء البطني والتحقق في ما إذا كان أي نقص في فيتامين د يمكن أن يرتبط بمستوى الأجسام المضادة الذاتية. تم شمول 46 مريضاً تم تشخيصهم مبكراً بمرض الداء البطني (11 ذكراً و 35 أنثى) على التوالي من مستشفى التمريض الخاص / بغداد، خلال الفترة من تموز 2018 إلى شباط 2019. كما تم إضافة عشرين شخصاً يتمتعون بصحة جيدة كمجموعة ضابطة. أظهر التوزيع العمري للمرضى أن 43.7% من المرضى تتراوح أعمارهم بين 10 و 20 سنة. من ناحية أخرى، كان 6 (13%)، 1 (2.1%) و 4 (8.6%) مرضى في الفئات العمرية 20-30، 30-40 و 40-50 سنة على التوالي. كانت الإناث أكثر من المرضى الذكور (66 و 34% على التوالي). كان لدى مرضى الداء البطني مستوى أقل بكثير من فيتامين (د) مقارنة بمجموعة التحكم ( $14.3 \pm 9.9$  و  $4 \pm 68$  نانوغرام / مل على التوالي). بالإضافة إلى ذلك، فإن 71.73% من مرضى الداء البطني يعانون من نقص فيتامين (د)، و 23.91% يعانون من كفاية فيتامين (د)، بينما كان لدى 4.34% من مرضى الداء البطني كان لديهم مستوى كافي من فيتامين (د). من ناحية أخرى، كان لدى 100% من الأشخاص في مجموعة التحكم مستوى كافي من فيتامين (د). ومع ذلك، لا يوجد فرق إحصائي في مستوى فيتامين (د) بين المرضى الذكور والإناث ( $10.08 \pm 15.3$  و  $8.9 \pm 12.58$  نانوغرام / مل على التوالي). يمكن الاستنتاج أن فيتامين (د) ينخفض بشكل كبير في مرضى الداء البطني.

**الكلمات المفتاحية:** الغلوتين، الداء البطني، فيتامين د، التهاب.

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#### **Introduction**

Celiac disease (CD) is an autoimmune disease which affect individuals with gluten-sensitivity (gliadin and glutenin). Celiac disease was known to be mostly prevalent in children with Caucasian ancestry. Nevertheless, subsequent data has demonstrated that it is a worldwide health problem and can also be prevalent in countries such as India, Brazil, Iraq, and South Africa [1-4]. Recent studies proved that there is a significant increase in the global incidence of celiac disease especially during the last two decades. They concluded that the prevalence of the disease can vary with age and sex, in addition to the location [2]]. Based on biopsy and serological test, the worldwide prevalence of celiac disease is estimated to be between 0.7 and 1.4% [3]. Nevertheless, more comprehensive studies are needed in Asia, Latin America and South America to give a more accurate estimates of celiac disease global occurrence [2].

In addition to genetic susceptibility, environmental factors are thought to play a role in the incidence of CD [5]. Along with the traditional gastrointestinal manifestations observed in CD patients, extra intestinal symptoms such as arthritis, depression, infertility, alopecia, fatigue and headache can also occur [6]. Occurring at any age, the gastrointestinal related complications are either associated with the direct mucosal lesions or nutrient deficiency which results from malabsorption. While the extra intestinal complications are related to immunological factors (reactivity to specified autoantigens) [7].

Three sequential small intestinal biopsies were required for the diagnosis of CD. However, nowadays less invasive approaches are preferred for CD diagnosis [8]. Detection of antibodies against tissue transglutaminase antigens (anti-TTG) is regarded as the most sensitive serological screening tool for CD. As such, several studies have reported a significant correlation of anti-tTG IgA titer with the staging of biopsy [9, 10]. The last two decades has witnessed an increasing interest in the role of vitamin D in the innate and adaptive immune response. Furthermore, vitamin D level has a potential role in the progression of a number of autoimmune diseases due to its role in the regulation of both dendritic and T-cells [6]. Weight loss and malabsorption along with mineral and vitamin deficiencies is a classic characteristic feature of

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CD. Among the vitamins that are affected is vitamin D. Studies in Europe, have reported vitamin D and subsequent osteomalacia in untreated CD patients [11]. As mentioned earlier, the vast majority CD published studies have been reported in European and North American populations which warrants the need for more studies to be conducted in other regions such as Asia and Africa. Thus the main aim of this study was to investigate the prevalence of vitamin D deficiency in newly diagnosed Iraqi CD patients.

#### **Patients and methods**

The present case-control study included 46 (35 females and 11 males) newly diagnosed CD patients. Patients were diagnosed by a clinician based on their clinical symptoms and the results of laboratory investigations (anti-TTG IgA >10.0 U/mL and anti-TTG IgG >9.0 U/mL). The age of patients ranged between 4 and 50 years. Blood samples were collected during the period from July (2018) to February (2019) from Special Nursing Hospital\ Baghdad. In addition, blood samples were also collected from 20 apparently healthy, age and gender matched individuals who served as a control group. This study was carried out after obtaining the relevant ethical approval. Verbal consent to participate in the study was obtained from all participants or their guardians.

A competitive electrochemiluminescence based assay was used for the quantitative measurement of total 25-OH vitamin D in the sera of CD patients and control. The assay was carried out according to the manufacturer's instructions (Roche Diagnostics, Mannheim - Germany). Depending on an earlier study, vitamin D concentration from 20 to 30 ng/mL was regarded to be insufficient, while concentrations less than 20 ng/mL was defined as a vitamin D deficiency [12].

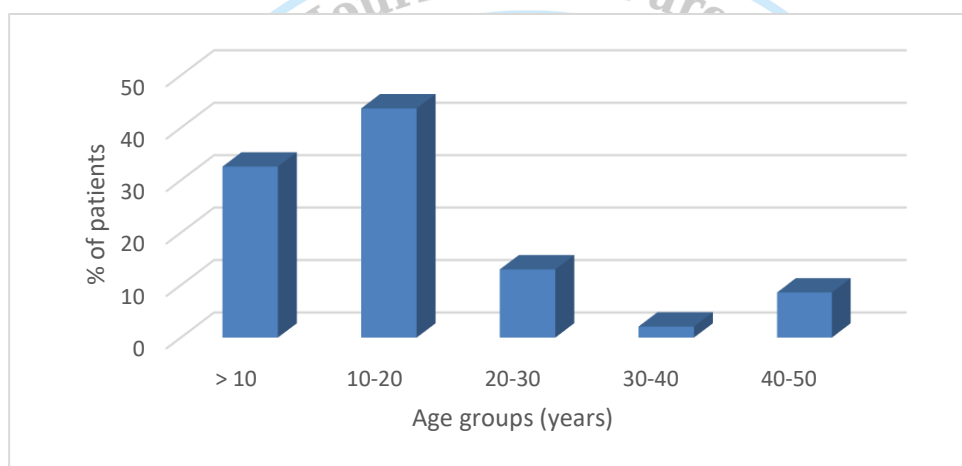
Statistical analyses: Microsoft Excel was used to calculate mean values and Standard deviation (SD). Comparison between patients and control was done using Unpaired Student T –test. While, simple linear regression analysis was used to investigate the association between variables. The results were regarded significant at  $P > 0.05$ , while  $P < 0.05$  was considered not-significant.

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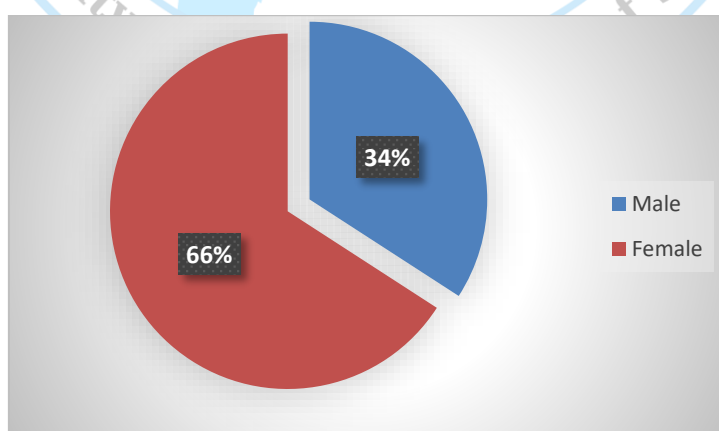
### Results

The age of patients ranged from 4 to 50 years with a mean age of  $15.9 \pm 11.6$  years. Patient's distribution according to age groups shows that 32.6 and 43.7% of patients were younger than 10 years old and between 10 and 20 years old respectively, while 13, 2.1 and 8.6% were in the age groups 20-30, 30-40 and 40-50 respectively as shown in figure 1.



**Figure 1:** Age groups of CD patients

The results showed that the percentage of females were more than males (66 % and 34% respectively) as shown in figure 2.



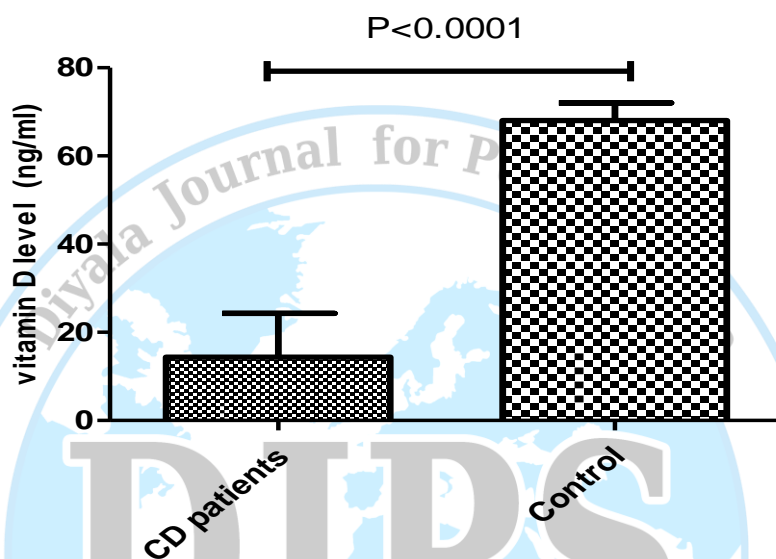
**Figure 2:** Distribution of CD patients according to gender



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A significant decrease ( $p < 0.0001$ ) was found in the level of vitamin D when compared to that of the control group as shown in figure 3.



**Figure 3:** Mean vitamin D level in CD patients and control

Out of the 46 CD patients included in the study, 2 (4.34%) had normal vitamin D level. However, 11 (23.91%) had vitamin D insufficiency and 33 (71.73%) had deficiency. All of the control group had normal vitamin D level, as shown in table 1.

**Table 1:** Vitamin D status in CD patients and control

Vitamin D Level	CD Patients (n=46)	Control (n=20)
Normal vitamin D level	2 (4.34%)	20 (100%)***
Vitamin D insufficiency	11 (23.91%)	0 ***
Vitamin D deficiency	33 (71.73%)	0 ***

\*\*\* denotes a highly significant difference ( $p < 0.0001$ )

Comparison between male and female patients revealed a non-significant difference ( $p = 0.46$ ) in the mean level of vitamin D as shown in table 2.

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**Table 2:** Comparison between male and female CD patients using serum vitamin D concentration (ng/dl).

Variable	male		female		P value
	Mean	( $\pm$ ) SD	Mean	$\pm$ (SD)	
Vitamin D level in serum (ng/ml)	12.58	8.9	15.3	10.8	0.46

Furthermore, analysis of results using simple linear regression revealed no significant association between the level of vitamin D and the level of anti-TTG IgA and anti-TTG IgG autoantibodies, ( $r^2 = 0.7$ ,  $p = 0.17$  and  $r^2 = 0.006$ ,  $p = 0.68$  respectively).

### **Discussion**

Celiac disease could be detected in both adults and children in Iraq [13, 14]. The age range of CD patients reported here is consistent to another study in Iraq [13]. The presented results demonstrated that the highest percentage (43.7%) of CD patients were between the ages of 10 and 20 years old.

Previous studies have reported that CD can be diagnosed at any age, however it is mostly present in either early childhood (from 9 months to 2 years of age) or in individuals between 30 to 40 years [15]. These findings contradict our results in which the highest percentage of CD patients were in the age group 10-20 years. This apparent disagreement could be due to the small number of patients, or to ethnic and genetic reasons. Underdiagnoses of the disease is a prominent feature of CD in the Middle East and this may also explain why the majority of patients were adolescents [16]. As with other autoimmune diseases, CD has classically been known to affect females more than males [3, 17]. The results reported in this study concur with this observation. Probable reasons for this female predominance is genetics, and that females in general tend to seek medical advice sooner than males [17]. Vitamin D has many immune regulatory characteristics and has a predicted role in the pathogenesis of autoimmune disorders. Vitamin D interacts with the immune system by inhibiting autoantibody production and co-stimulatory molecule secretion, in addition to suppression of dendritic cells differentiation and

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thus contributes to suppression of autoimmune pathways [18, 19]. This explains why CD patients had significantly low vitamin D level. Similar results were observed by other researchers [20-22], and it is even recommended that newly diagnosed CD pediatric patients check their vitamin D level, and get subsequent assessment during follow-up checks if deficient [23]. A previous study has documented that 20-50% of CD patients suffer from low vitamin D levels [24].

The increased percentage of vitamin D deficiency reported in the current study could be related to the different patient's sample size between studies, in addition to the different groups of CD patients included in their study. Malabsorption of vitamin D, together with lactose intolerance caused by elimination dietary of milk and dairy products are postulated reasons for vitamin D deficiency in patients with CD [25]. Nevertheless, a published study has concluded that treatment with a gluten-free diet leads to sub-optimal vitamin D levels in CD patients [21].

Antibodies against transglutaminase autoantigen is considered as the hallmark of the disease in CD patients [26], and thus the absence of any association between vitamin D level and the concentration of autoantibodies (anti-TTG IgA and anti-TTG IgG) observed in this study suggests that vitamin D deficiency may be caused by malabsorption rather than being an etiological factor of CD occurrence which has been previously suggested [27]. The absence of any significant difference between male and female CD patients in vitamin D level may also be explained by, the fact that malabsorption lies behind this deficiency. A similar study in Saudi Arabia has linked severe deficiency of vitamin D with CD and suggesting that patients with low levels of vitamin D should be screened for CD [28].

It has been suggested that genetic polymorphism of vitamin D receptors in CD patients could be the main cause of vitamin D deficiency. Nevertheless, Lu and colleagues have reported no difference in the genotypes of vitamin D receptors between CD patients and control [29].



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### Conclusions

A significant reduction in vitamin D level was found among celiac disease patients as comparison with healthy individuals. Furthermore, no association was found between the levels of tissue transglutaminase antibody (IgA and IgG) and the level of vitamin D in celiac disease patients suggesting that the level of vitamin D was not associated with the severity of the disease. Finally, the investigation whether gluten-free diet has any effect on the level of vitamin D in CD patients could be recommended in future studies.

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