



# Adult Celiac Disease: Patients Are Shorter Compared with Their Peers in the General Population

Abbas Esmailzadeh<sup>1</sup>, Azita Ganji<sup>1\*</sup>, Ladan Goshayeshi<sup>1</sup>, Kamran Ghafarzadegan<sup>2</sup>,

Mehdi Afzal Aghayee<sup>1</sup>, Homan Mosanen Mozafari<sup>1</sup>, Hassan Saadatniya<sup>1</sup>,

Abdolrasol Hayatbakhsh<sup>1</sup>, Vahid Ghavami Ghanbarabadi<sup>3</sup>

1. Gastroenterology and Hepatology Research Center, Mashhad University of Medical Sciences, Mashhad, Iran
2. Mashhad Pathobiology Laboratory, Mashhad, Iran
3. PhD Candidate in Biostatistics, Department of Epidemiology and Biostatistics, School of Health, Tehran University of Medical Sciences, Tehran, Iran

## ABSTRACT

### BACKGROUND

Delay in diagnosis of celiac disease (CD) occurs frequently, although its consequences are mostly not known. One of the presented symptoms in pediatric patients with CD is the short stature. However, far too little attention has been paid to physical features including height of adult patients with CD. This study was undertaken to evaluate whether patients suffering from CD are shorter in comparison with the general population without CD. As well, we evaluated probable correlations between demographic and physical features, main complains, serum anti tTG level, and intestinal pathology damage between short (lower quartile) versus tall stature (upper quartile) patients with CD.

### METHODS

This was a retrospective cross-sectional study on 219 adult patients diagnosed as having CD in the Celiac Disease Center, between June 2008 and June 2014 in Mashhad, Iran. The exclusion criteria were ages less than 18 and more than 60 years. Height was compared with a group of 657 age- and sex-matched control cases from the healthy population. The probable influencing factors on height such as intestinal pathology, serum level of anti-tissue transglutaminase (anti-tTG), serum vitamin D, and hemoglobin level at the time of diagnosis were assessed and were compared in short (lower quartile) versus tall stature (upper quartile) patients with CD.

### RESULTS

Both male (n=65) and female (n=154) patients with CD were shorter than their counterpart in the general population (males: 168.5±8.6 to 171.3±7.2 cm,  $p < 0.01$  and females: 154.8±10.58 to 157.8±7.2 cm,  $p < 0.01$ ). Spearman linear correlation showed height in patient with CD was correlated with serum hemoglobin ( $p < 0.001$ ,  $r=0.285$ ) and bone mineral density ( $p < 0.001$ ) and not with serum vitamin D levels ( $p=0.024$ ,  $r=0.237$ ), but was not correlated with anti-tTG serum levels ( $p=0.97$ ).

CD patients with upper and lower quartile of height in men and women had no significant difference in the anti-tTG level and degree of duodenal pathology (Marsh grade). Anemia as main complaint was more prevalent in shorter versus taller men.

### CONCLUSION

Adults with CD are shorter compared with healthy adults. There is a direct correlation between height and anemia and bone mineral density. This finding highlights the importance of early detection and treatment of CD.

### KEYWORDS

Celiac disease, Height, Vit D level, Anemia

#### \* Corresponding Author:

Azita Ganji, MD

Gastroenterology and Hepatology Research Center, Mashhad University of Medical Sciences, Mashhad, Iran  
Telefax: + 98 513 2280736  
Email: ganjia@mums.ac.ir

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## INTRODUCTION

Celiac disease (CD) is a chronic immune-based enteropathy in genetically predisposed children and adults, which occurs due to the presence of gluten—a protein present in rye, barley, and wheat. CD can be treated by eliminating gluten from the patients' diet. The prevalence of CD is approximately 1% worldwide<sup>1,2</sup> and is common in the Middle Eastern countries, particularly in Iran.<sup>3</sup> In two different studies on blood donors and general population in Iran the prevalence estimation of CD were between 0.5% to 1%.<sup>4,5</sup>

The clinical features of CD vary, ranging from classic presentation of malabsorption, weight loss, and steatorrhea, to a wide range of other signs and symptoms that go well beyond the gastrointestinal tract.<sup>6-8</sup> Most of the patients with CD are diagnosed by screening high-risk population, i.e short stature, being directly related to patients with CD, people with type 1 diabetics, and inflammatory bowel syndrome (IBS).<sup>9,10</sup>

The delay in the diagnosis of CD is often due to lack of obvious symptoms. Furthermore, there are very few gastrointestinal clinical symptoms in undiagnosed individuals.<sup>11</sup> Recent studies suggest that 32.6±13.2 years are the mean age for diagnosis of CD while diagnosis of patients over 50 years old makes up 11.3% of the total diagnosed patients with CD.<sup>12</sup> According to reports of Cosnes and colleagues the children of both sexes with undiagnosed CD were shorter in stature than those with diagnosed CD or children without CD.<sup>13</sup> Another such study showed that only men with undiagnosed CD were shorter and not women compared with the general population.<sup>14</sup> Similarly, other studies suggested that only women with undiagnosed CD were shorter.<sup>15</sup> There are few studies about the influencing factors and their correlation with malnutrition, severity of CD base on pathology, and anti-tTG levels.

This study was undertaken to evaluate whether patients suffering from CD are shorter in comparison with the general population without CD. Additionally we evaluated probable correlations

between demographic and physical features, main complaints, serum anti-tTG level, and intestinal pathological damage between short (lower quartile) versus tall stature (upper quartile) patients with CD.

## MATERIALS AND METHODS

### Research design and setting:

This was a two-group, cross-sectional study conducted in patients referred to Celiac Disease Center for diagnostic evaluation from 2008 to 2014 and a control group with cluster sampling of general population in Mashhad University of Medical Sciences.<sup>16,17</sup>

### Sampling

#### Sample size:

Two population based studies in Mashhad by cluster sampling methods were done on 35-65 years old and on 15-35 years old individuals in 2010-11<sup>16,17</sup> and we selected 657 individuals from these studies as the healthy control group and 219 for the patients with CD group, determined with 99% confidence interval and 95% power.

#### Sampling method:

Based on our previous study on general population of Mashhad aged 15-65 years, we had 815 cases of age-, and sex-matched to our patients with CD with negative tTG who were selected as control group. Individuals aged less than 18 years and more than 60 years were excluded. After applying inclusion and exclusion criteria finally 657 (3 times of patients with CD group) cases for control group were selected randomly. Patients with confirmed CD were selected by means of purposive sampling.

Of the 301 patients with CD, we also excluded patients aged less than 18 and more than 60 years. In the celiac group 48 patients aged less than 18 years, 3 patients aged over 60 years, 17 patients with tTG titer below 30 (UN/mL), or with missed data, and 14 patients with Marsh=<1 were excluded. Finally 219 patients in celiac group were included in this study. The results are shown in tables 1 and 2.

So, the study was conducted on two groups with confirmed CD (case group) and the healthy popula-

tion (control group).

#### **Selection criteria:**

Consecutive patients referred to Celiac Disease Center for diagnostic evaluation of CD were considered eligible if CD was clinically suspected on the basis of having signs or symptoms of malabsorption, recurrent diarrhea, malnutrition, or dyspepsia and bloating (classic presentation), or anemia, and osteopenia, (non-classic presentation) and having a positive serology of anti-tTG IgA that was assessed by enzyme-linked immunosorbent assay (ELISA), Kit (Euro immune, Germany) in a research laboratory, and positive pathological damage of duodenum.

Our inclusion criteria were age more than 18 and less than 60 years. Patients were excluded if they had score  $\leq 1$  in Modified Marsh Classification or tTG level below 30 (UN/mL), which is one and half time more than upper normal limit.

#### **Data collection:**

Collected data were age, sex, height, weight, anti-tTG level, and Modified Marsh Classification score.

Firstly, for all high clinically suspected patients for CD, serology screening was done and if they had more than upper limit of anti-tTG IgA, endoscopy and duodenal biopsy was done. At least three duodenal biopsy samples were taken by expert gastroenterologists, and one professional gastrointestinal pathologist made the pathology report. The Modified Marsh Classification of histological findings was used to classify the mucosal lesions for diagnosis of CD in suspected patients.<sup>18</sup> Anti-tTG Kit (Euro immune, Germany) was used to counter check the anti-tTG (Ig A) level in a single laboratory. CD was confirmed if the patients had anti-tTG (Ig A) level  $>30$  IU and Marsh  $>1$ .

Basic information such as age and sex was recorded for all the patients with confirmed CD. Then, anthropometric measurements, including height, weight, and body mass index (BMI) were done for CD patients. The measurement of both height and weight were performed by one trained and educated assistant in our clinic. Body weight measuring was

done by Seca scales (Seca, 22089 Hamburg, Germany). BMI was also calculated by dividing weight (kilograms) to squared height (meter). The methodology of height, weight, and BMI determination was the same in healthy control group.

#### **Research ethics:**

The study was approved by the Ethics Committee of Mashhad University of Medical Sciences, and all the patients provided written informed consent before they were enrolled.

#### **Statistical analyses:**

The data were analyzed using SPSS software version 17.0.1 (SPSS Inc, Chicago). Normal distribution of the data was assessed by using Kolmogorov-Smirnov test. We compared the height, weight, and BMI of our patients with the general population and compared high quartile with low quartile of height in patients with CD.

The analysis of continuous variables was made using the Student t test and the Pearson  $\chi^2$  test was used for discrete variables. The determination of significance for every analysis was set at  $p < 0.05$  (two tailed).

#### **RESULTS:**

Finally, 219 patients with a confirmed diagnosis of CD, and 657 healthy controls were studied in this trial. The groups were matched based on sex and age (table 1).

By using Man-Whitney test, results revealed that both male and female adults having CD were shorter, less weighed, and with a less BMI in comparison with their peers of both sexes (table 2).

Adults having CD were significantly shorter than the healthy control group (patients with CD:  $158.96 \pm 11.82$  cm, versus controls:  $161.99 \pm 9.51$  cm,  $P < 0.001$ ). Also, mean weight was lower in the CD group versus healthy control group (CD:  $57.60 \pm 13.12$  kg, versus control:  $68.98 \pm 13.89$  kg,  $p < 0.001$ ). Correspondingly, BMI was significantly lower in the CD group compared with the healthy control group (CD:  $23.16 \pm 10.14$  kg/m<sup>2</sup> versus control:  $26.34 \pm 5.30$  kg/m<sup>2</sup>,  $p < 0.001$ ) (table 2).

Moreover, the difference between the mean height, weight, and BMI between the two groups was also sig-

**Table 1: Comparison of age and sex between patients with celiac disease and control group**

Variables	Celiac disease group (n=219)	Healthy control group (n=657)	p value	Test
Age, years (mean±SD)	35.48±11.61	35.12±10.74	0.68	Two independent t test
Male, n (percent)	65 (30%)	197 (30%)	0.13	Pearson Chi-square test
Female, m (percent)	154 (70%)	460 (70%)		

**Table 2: Comparison of weight, height, and body mass index between patients with celiac disease and control group**

Variables	Control group (n=657)	Celiac group (n=219)	p-value*(95%CI of the difference)
Weight(kg) mean±SD	68.98±13.89	57.60±13.12	<0.001 (9.24-13.53)
Height(cm) mean±SD	161.99±9.51	158.96±11.82	<0.001 (1.43-4.62)
BMI(kg/m <sup>2</sup> ) mean±SD	26.34±5.30	23.16±10.14	<0.001 (2.12-4.26)

**Table 3: Comparison of weight, height and BMI between patients with celiac disease and control group according to sex**

Variables	Male group (n=262)		P value (95% CI)	Female group (n=614)		p value (95% CI)
	Control group (n=197)	Celiac group (n=65)		Control group (n=460)	Celiac group (n=154)	
Age (years), mean±SD	35.0±10.1	32.7±14.9	0.176 (-1.0 – 5.6)	33.9±12.1	32.7±12.7	0.324 (-1.20 – 3.64)
Weight (kg), mean±SD	75.3±13.93	64.3±12.5	0.001 (7.11-14.8)	66.3±13	54.8±12.4	0.001 (9.02 – 13.84)
Height (cm), mean±SD	171.3±7.2	168.5±8.6	0.00 (0.629-4.97)	157.8±7.2	154.8±10.5	0.001 (1.46-4.52)
Body mass index (kg/m <sup>2</sup> ), mean±SD	25.5±4.4	22.3±3.5	0.001 (2.14-4.31)	26.7±5.6	23.5±11	0.001 (1.74-4.62)

nificant in both male and female sexes separately (table 3).

Kruskal-Wallis test showed that severity of duodenal pathology (Marsh classification) was not correlated with the height ( $p = 0.09$ ). A correlation between height and hemoglobin level ( $p < 0.001$ ,  $r = 0.163$ ) was detected.

By using Fisher exact test there was no correlation between pathology in low and high quartil of height ( $p = 0.51$ ), and by Pearson Chi-Square test no difference between height and low quartil of height in vit D level was found ( $p = 0.92$ ).

CD patients having lower quartile of height (56 patients [25.5%]) in both men and women had no significant difference in anti-tTG level, degree of duodenal pathological damage with high quartile of height (52 patients [23.7%]). Anemia as main complaint was more prevalent in shorter versus taller men ( $p = 0.013$ ). Mean hemoglobin in high quartile of height was 13.5 g/dL compared with 10.3 g/dL in low quartile of height (table 3). There was a significant difference in bone mineral density in high and low quartil of height. Spine osteoporosis was 6% in high quartil and 32% in low quartil of height ( $p < 0.001$ ). Femoral osteoporosis was 2.3% in high and 30% in low quartil of height ( $p < 0.002$ ).

Mode of presentation had no effect on final height. And patients with classical presentation of CD such as diarrhea, malabsorption, and weight loss had no difference in height compared with patients with non-classical presentations and both groups had shorter height compared with the control group.

We had another assessment in screening CD by anti-tTG and healthy general population and there was no significant difference between height in them. It shows that height is probably lower in symptomatic CD.

#### DISCUSSION:

Shorter height as a complication associated with childhood CD is quite well established.<sup>19,20</sup> Although in most of the cases early intervention with gluten free diet enable some catching up growth<sup>21</sup>, the real pathogenesis behind the short height related to CD is still not very clear.<sup>22</sup> The process of growth is indeed a highly complex process that depends on numerous intrinsic factors (like hormones i.e. growth hormone [GH], thyroid hormone, androgens, estrogens, gherlin, and insulin), and also on extrinsic factors such as nutrition. Deficiency and derangement of any of these factors can lead to a shorter height.<sup>14</sup> Nevertheless, delay in linear growth in patients may be associated

with resistance to GH 22 or due to GH deficiency.<sup>23</sup> This suggestion is based on the fact that there is elevated or normal GH levels in CD patients along with low levels of insulin like growth factor-I (IGF-I).<sup>22</sup> Other studies emphasize on antipituitary autoantibodies (APA) as a case of autoimmune hypophysitis in the somatotroph cells.<sup>24</sup>

Sonti and colleagues showed that among adult patients with CD who reached to their final height before diagnosis, only men were shorter compared the general population 14 and there was an inverse relation between the height of the adult male patients with CD and their age at the time of diagnosis.<sup>25</sup> In our study both men and woman who were diagnosed after 18 years old were shorter compared with their peers in the general population. There are very few earlier reports available on the final height of patients suffering from CD with contradictory results. The reports of Cacciari and co-workers 6 suggested normal height of patients diagnosed with CD in their adulthood, whereas Weiss and others reported that the final height of the CD patients was comparable to that of the general population.

A total of 184 CD patients aged 18-88 years (56 men) were studied by Cosnes and colleagues. They reported that both men and women with CD diagnosed in adulthood were shorter than their control or CD patients who were diagnosed in childhood.<sup>13</sup> An older study showed that patients with CD who were more than 20 years old and received gluten free diet(GFD) were not shorter in comparison with the control group, but weighted less.<sup>26</sup> In a recent study in Finland, no major differences in height were observed between CD patients and the control group in either sex. However, when analysis of the subgroups was taken into consideration shorter height was observed in a few older but not younger birth cohorts <sup>27</sup> but in our study we excluded patients aged more than 60 years to delete the effect of aging on height.

The deficiency in minerals and vitamins are common in newly diagnosed patients with CD.<sup>28</sup> In a recent study in Netherland zinc deficiency was noted in 67% of the patients and iron deficiency in 46% of patients with CD, and 32% of them were suffering from anemia.<sup>29</sup> On the other hand, atypical presentations of CD have amplified over the preceding two decades.<sup>7</sup> In a recent study in these area non-typical complaints such as dyspepsia, anemia, and osteopenia were more common than typical symptoms.<sup>12</sup>

In our study there was no difference in height between

patients with classical or typical presentations and patients with non-classical presentations.

In our study, patients in low quartile of height compared with the high quartile of height had more anemia (mean hemoglobin level was 13 g/dL in high compared with 10 g/dL in low quartile of height [ $p < 0.001$ ]) and had vitamin D deficiency (vitamin D < 30 ng/dL). We found that these nutritional deficiencies correlated with final height.

The present study clearly suggested that the mean height of adult patients was correlated with low vitamin D serum levels and anemia. And also in CD patients, height was not correlated with serum anti-tTG level and severity of duodenal pathological damage (Marsh). So this result suggests that malnutrition may be the main cause of short stature in our CD patients and can be due to delay in diagnosis. It is quite well established that there may be more than a decade delay in the diagnosis of CD.<sup>30</sup> The diagnosis of CD is often delayed in case of patients with less symptoms and in individuals with little gastrointestinal symptoms like nausea, vomiting, or abdominal bloating.<sup>11</sup> In our study male CD patients with lower quartile height had more anemia as chief complaint than patients with higher quartile height. Sonti and colleagues found comparing results only in men with CD.<sup>14</sup>

Iron deficiency anemia was most frequent in patients with untreated CD in their past, but it is still the commonest recurrent extraintestinal symptom.<sup>31</sup> It has to be noted that mild or moderate pathophysiological abnormalities do not necessarily suggest mildness of the disease.<sup>32</sup> In our study there was also no correlation between histopathological abnormalities (Marsh grade) and final height in CD.

Deficiency in minerals or vitamins are quite common in patients suffering from CD. So patients with untreated CD who are diagnosed at adult stage may have shorter height compared with patients with early diagnosis who received treatment at their childhood. This further highlights the significance of early diagnosis and treatment of CD with proper strategies based on diet for better treatment of malabsorption that may lead to normal height in the patients with CD.

The importance of this study lies in the fact that we performed the analysis of the measured variables like height and weight and densitometry in a large number of CD patients. The examinations were done in a single clinic with the help of trained researchers and under the

guidance of specialist gastroenterologists to complete the questionnaire.

The CD patients were well matched demographically to the comparison group. Also, we assessed some influencing factors on height in order to investigate the pathogenesis of shorter height in relation to CD.

However, we did not measure GH, insulin, or other influencing factors. So in future a thorough epidemiological survey should be carried out to confirm these findings and investigate the etiology of short stature in CD.

This study is the first of its kind to assess the height in adults patients with CD in comparison with healthy controls.

Shortness of height is an eminent characteristic of childhood CD. However, we found that in comparison with the general population, adults with CD are considerably shorter. This shortness can also be correlated with hemoglobin level and bone mineral density, but it does not correlate with the severity of CD as a function of duodenal pathology and serum anti-tTG level. So malnutrition may be the main cause of short stature in adult CD patients long before the onset of symptoms.

#### CONFLICT OF INTEREST

The authors declare no conflict of interest related to this work.

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