Men with celiac disease are shorter than their peers in the general population

Rajiv Sonti, Benjamin Lebwohl, Suzanne K. Lewis, Hussein Abu Daya, Heather Klavan, Kathleen Aguilar and Peter H.R. Green

Objective **Late diagnosis of celiac disease (CD) is increasingly common, the implications of which are largely unknown. Although short stature is a common sign of childhood CD, the data on the height of adult CD patients is conflicting. This study investigates the final height of men and women diagnosed with CD in adulthood and attempts to identify influencing factors.**

Patients and methods **We performed a cross-sectional study of 585 adults at the Celiac Disease Center at Columbia University, comparing their height with the control population (NHANES). Patients were included if they were older than 18 years of age at diagnosis and if baseline height and weight were available. In addition, we examined for differences in demographic and physical features, mode of presentation, and concomitant illnesses in shorter versus taller celiac patients.**

Results **Men ($n=162$) with CD diagnosed in adulthood were shorter than men in the general population (CD: 169.3±10.5 vs. 177.3±7.0 cm, $P<0.01$) whereas women ($n=423$) were not (CD: 166.3±9.4 vs. 163.2±6.7 cm). There were no statistically significant differences in age at diagnosis, BMI, concomitant autoimmune illnesses (hypothyroidism, type I diabetes, dermatitis herpetiformis), or mode of presentation in shorter versus taller CD patients of either sex. Hemoglobin was associated with short stature in CD men (short: 13.9 g/dl, tall: 14.6 g/dl; $P=0.01$), but not women (short: 12.9 g/dl, tall: 13.0 g/dl, $P=0.41$).**

Conclusion **Short stature is a well described phenomenon in pediatric CD with the potential for 'catch-up growth' on a gluten-free diet. However, among adults with CD who had attained final height before diagnosis, we found that men, not women, are shorter relative to the general population.** ***Eur J Gastroenterol Hepatol*** **00:000–000** © **2013 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

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Department of Medicine, Celiac Disease Center, Columbia University Medical Center, New York, New York, USA

Correspondence to Peter H.R. Green, MD, Department of Medicine, Celiac Disease Center, Columbia University Medical Center, Harkness Pavilion, 180 Fort Washington Avenue, Suite 934, New York, NY 10032, USA
Tel: +1 212 305 5590; fax: +1 212 395 3738; e-mail: pg11@columbia.edu

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Introduction

Celiac disease (CD) is an autoimmune disorder precipitated by the ingestion of gluten in genetically susceptible individuals [1]. The clinical features are extremely varied – the classic presentation of a malnourished young child with chronic diarrhea is increasingly rare and the average age of diagnosis is increasing [2]. Implications of later diagnosis, often delayed until adulthood, almost certainly include lower BMI [3]. However, the effect of the disease on height is less well characterized and there are discrepancies in the literature on the final adult height of CD patients.

Poor growth is a common manifestation of pediatric CD with the potential for variable degrees of 'catch-up growth' (compensatory growth after a period of nutritional deficiency during which growth rate greatly surpasses average growth rate) upon initiation of a gluten-free diet (GFD) [4]. Variability may be related to GFD adherence and age at diagnosis, delays in which can lead to slower and more incomplete catch-up growth [5–7]. The impact of diagnosis delayed until adulthood, however, is not clear. Some reports document final height equivalent to the population [8–10], others reduced final height [11], and interestingly, some show reduced height only in men (or greater degree of height loss in men as opposed to women) [11–13], whereas still others show reduced height only in women [14].

The purpose of this study was to investigate the height of patients with CD diagnosed after having achieved their adult height. We additionally attempted to determine whether there are correlations between other demographic and physical features, presenting signs or symptoms, or medical comorbidities between CD patients of short versus tall stature.

Patients and methods

We analyzed the prospectively maintained database of patients from the Celiac Disease Center of Columbia University. On initial visit, permission is obtained from patients for anonymous inclusion into the database, at which point basic demographic features, physical measurements (measured at the clinic), and medical history (in particular how it relates to CD) are recorded. For individuals first seen after the initial diagnosis, effort was made to obtain height and weight data from the preceding institution; often this

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information was unavailable. Inclusion criteria for this study were patients with biopsy-confirmed CD diagnosed since 1990, age of at least 18 years at the time of diagnosis, and baseline height and weight available. Comorbid illness specifically linked to short stature was rare in this group and we did not specifically exclude on the basis of this in an effort to minimize sampling bias. Eighteen was chosen as the cut-off age because it, for the most part, represents the end of linear growth [15]. The mode of CD presentation was recorded as diarrheal, anemia, osteoporosis, incidental on endoscopy, screening [usually because of diagnosed close relatives or presence of type I diabetes mellitus (T1DM) or autoimmune thyroiditis] or 'others' (generally extraintestinal manifestations such as arthralgias or infertility). Initial diagnosis made as a result of workup of chronic diarrhea was classified as 'typical' and the remainder as 'atypical'. Concomitant illnesses were also recorded including T1DM, dermatitis herpetiformis, and autoimmune hypothyroidism.

We compared the height of our patients to the US population by using the latest National Health and Nutrition Examination Survey (NHANES). The NHANES program surveys and examines roughly 5000 people from all over the USA every year and the measurements obtained are the basis for national standards and are widely used in epidemiologic and health science research. Although our cohort spans patients diagnosed over two decades from one center, there has not been a significant change in the height of the population during that time [16] and significant regional differences in height within the USA have not been documented [17]; hence, we considered it appropriate to use only the latest publically available NHANES survey (2009–2010). The vast majority of our cohort is whites, so we restricted the NHANES dataset to whites aged older than 18 years.

To investigate the potential differences between shorter and taller celiac patients, we divided both sexes into two groups by height: bottom tertile versus the taller two-thirds. The mode of presentation, presence of concomitant illnesses, duration of symptoms, hemoglobin within 1 year of diagnosis, and severity of villous atrophy (by Marsh Classification) were compared between each group. We partitioned groups in this way to isolate the shortest CD patients and facilitate identification of any variables correlated with short stature. Duration of symptoms was self-reported and only relevant for patients who originally presented with diarrhea.

Continuous variables were analyzed by the Student *t*-test and discrete variables by Pearson χ^2-test. For each analysis, significance was determined at the level of P less than 0.05 (two-tailed). The study was approved by the Columbia University's Institutional Review Board.

Results

At the time of data analysis, 585 patients of a total of 1580 fulfilled the inclusion criteria. Of those excluded, 346 were diagnosed before 18 years, 178 were diagnosed before 1990, and 471 did not have height recorded at the time of diagnosis. Women predominated (72.3%) and 76.8% were diagnosed after the year 2000. In 2009–2010, NHANES surveyed 5906 individuals over the age of 18 years, 2667 of whom are whites: 1364 women and 1303 men (Table 1).

Compared with the control group (NHANES), men with CD were shorter (CD: 169.3 ± 9.4 vs. 177.3 ± 7.0 cm, $P < 0.01$) whereas women were not (CD: 166.3 ± 9.4 vs. 163.2 ± 6.7 cm). In fact, women in our cohort were slightly taller, a finding that was statistically significant ($P < 0.01$). One obvious outlier value was present (a 132-cm tall male) – but in both sexes there were similar mean and median values of height (men: median, 170; mean, 169.3; women: median, 165.4; mean, 166.3). As expected, the distribution of height in our population was similar to a normal distribution (Fig. 1a and b). Average BMI was significantly lower in the CD population as opposed to the control group in both sexes: men (CD: 23.1 vs. 28.7, $P < 0.01$), women (CD: 23.2 vs. 28.8, $P < 0.01$).

The CD patients were divided into two height groups: one with the shorter one-third of patients (53 men, 144 women) and the second with the taller two-thirds (109 men, 279 women). As can be seen in Table 2, there were no differences between these groups in age at diagnosis, average BMI, percentage with typical presentation, percentage with a more severe degree of villous atrophy (partial vs. subtotal or total) or duration of symptoms before diagnosis in either sex. In addition, there was no association between height and concomitant autoimmune hypothyroidism, T1DM or dermatitis herpetiformis in either sex. We did find that the shorter CD men had lower average hemoglobin, a pattern not found in women. Overall, both men and women had lower hemoglobin values than the control population (CD: women 12.9 vs. 13.6, $P < 0.01$; CD: men 14.4 vs. 15.2, $P < 0.01$)

Discussion

In this large cohort of patients with CD, we found that men diagnosed after attaining final adult height are shorter than an age-matched and race-matched national reference population, a pattern not observed in women. No other physical or demographic feature, presenting sign or symptom, or concomitant illness or condition correlated to height within the CD patients. Hemoglobin recorded near diagnosis, however, was lower in shorter men. Overall, the entire CD cohort had lower hemoglobin and BMI values than the reference population.

Sex discordance in adult height among CD patients has been described previously. In a recently published study from Turkey, an inverse correlation was noted between age at diagnosis and final attained height in men (not in women) in a cohort of 290 CD patients – a finding that led the authors to conclude that delayed diagnosis can lead to shorter height in men but not women [10]. However, the patients of both sexes were similar in

height to the general population overall, and height was self-reported as opposed to measured. A 1991 Italian study of 95 CD patients diagnosed in adulthood found that men who had gastrointestinal symptoms in childhood were shorter than their peers in the population by an average of 3 cm, but women with gastrointestinal symptoms were not [12]. This was not statistically significant, however; and there were only 25 men included in this analysis (70 women). Similarly, a study published in 2002 from France found that both CD men and women who were symptomatic but undiagnosed in childhood were shorter than matched controls, but the difference was greater for men (a difference of 5 vs. 3 cm), a finding that was statistically significant [11]. In both studies, final adult height was only affected by late diagnosis if there were symptoms in childhood.

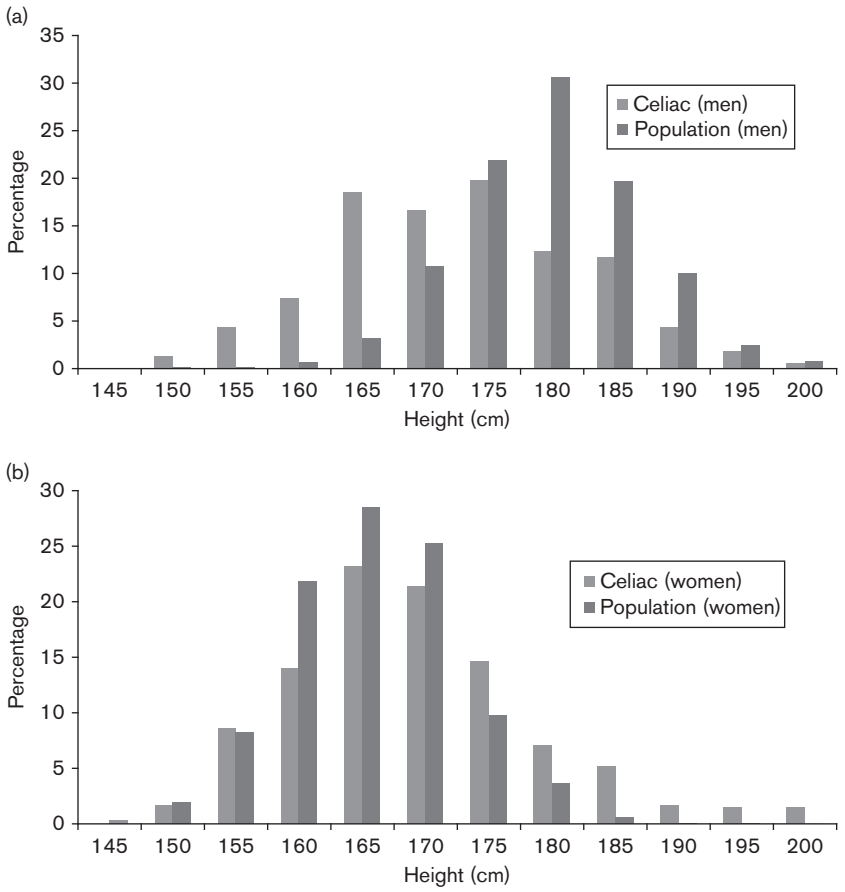
Table 1 **Group characteristics**

	Celiac disease		NHANES	
	Men	Women	Men	Women
n	162	423	1303	1364
Average age (years)	42.4	45.4	48.4	47.7
Average BMI	23.1	23.2	28.7	28.8

Other studies find no such difference in the height of patients with CD. For example, a 1991 study of 161 CD patients older than 20 years of age on a GFD from the Danish registry found that although CD patients weighed less than a control group, they were not shorter [9]. In a recently published large analysis of 1084 CD patients from 1920–1989 in Finland, there was no overall height difference of CD patients of either sex in comparison to era-matched population controls [8]. Although representing only a subset of those studied, in two particular historic birth cohorts, men with symptoms and screening-detected women were shorter.

Growth is a complex process dependent on a host of intrinsic factors [hormones including growth hormone

Fig. 1



(a) Histogram of height of men with celiac disease (CD) and the control population. CD men were shorter (CD: 169.3±10.5 vs. 177.3±7.0 cm, $P \leq 0.01$). (b) Histogram of height of women with celiac disease and the control population. CD women were slightly taller (CD: 166.3±9.4 vs. 163.2±6.7 cm, $P < 0.01$).

Table 2 Celiac cohort bottom tertile vs. taller two-third of height

	Women		*P*-value	Men		*P*-value
Height (total number) (cm)	147–160 (144)	161–198 (279)	–	132–164 (53)	165–196 (109)	–
Age at diagnosis (years)	46.3	44.9	0.39	40.2	43.4	0.23
Average BMI	23.3	23.0	0.53	23.7	23.0	0.35
Typical presentation (diarrhea) [*n* (%)]	51 (35.4)	98 (35.1)	0.24	19 (35.8)	36 (33)	0.72
Atypical presentation [*n* (%)]	93 (64.6)	181 (64.9)	–	34 (64.2)	73 (67)	–
Partial villous atrophy	39	90	–	12	37	–
Total or subtotal villous atrophy [*n* (%)]	90 (69.8)	150 (62.5)	0.17	34 (73.9)	61 (62.2)	0.19
Average Hb (g/dl)	12.9	13.0	0.46	13.9	14.6	0.01
Duration of symptoms (years)	5.82	5.53	0.87	2.93	5.33	0.26
Hypothyroidism [*n* (%)]	16 (11.1)	32 (11.5)	0.91	5 (9.4)	6 (5.5)	0.35
T1DM [*n* (%)]	2 (1.4)	9 (3.2)	0.26	2 (3.8)	3 (2.8)	0.72
Dermatitis herpetiformis [*n* (%)]	5 (3.5)	17 (6.1)	0.25	3 (5.7)	6 (5.5)	0.97

Celiac disease (CD) men and women were divided into two groups by height: shorter one-third vs. taller two-thirds. Age, BMI, mode of presentation, degree of atrophy, concomitant autoimmune illness, and hemoglobin (Hb) were compared. The only significant association was a lower Hb level in shorter CD men. Of note, the duration of symptoms was available for 74% of CD patients presenting with diarrhea, Hb (g/dl) measured within 1 year of diagnosis for 80.5% of patients, and histologic grade at diagnosis for 88% of patients.

(GH), thyroid hormone, androgens, estrogens, and insulin] and extrinsic factors (namely nutrition), with derangements in any of these potentially leading to short stature. The pathogenesis of short stature in pediatric CD remains speculative. One theory involves GH axis dysfunction at varying levels including frank GH deficiency [18,19], GH insensitivity [20], or lower levels of downstream insulin-like growth factor-I (IGF-I), IGF-II, IGF binding protein-3 (IGFBP-3), and higher concentration of IGFBP-2 in CD patients as opposed to controls [21–23]. These abnormalities are almost certainly due in part to malnutrition; caloric deprivation alone can lead to abnormal GH levels [24]. However, increased serum concentrations of the proinflammatory cytokines interleukin-6 (IL-6), TNF-α, INF-γ, IL-4, IL-10, and IL-18 [25,26] may also play a role. Moreover, a few experiments demonstrate positive antipituitary antibodies in newly diagnosed CD patients, suggesting a possible autoimmune involvement of the pituitary gland in such patients [27,28], perhaps leading to reduced levels of IGF-I [27]. Many of these changes normalize upon the institution of a GFD, coinciding with catch-up growth [25]. In addition, long-standing osteoporosis as a result of nutrient malabsorption in undiagnosed CD may eventually lead to lost height.

Although seemingly plausible, these mechanisms do not explain sex discordance in final height. Our data lead us to two possible hypotheses: either men have more severe disease or the growth process is different in men, leaving them more susceptible to malnutrition or inflammatory changes of CD. Although CD has equal sex seroprevalance [29], many more women are diagnosed. There are many possible reasons for this; regardless, the men who actually carry a diagnosis may represent only the tip of the iceberg and have more serious illness. It has been previously reported that men may have more severe manifestations of malabsorption, as evidenced by lower total cholesterol and lower T and Z distal radius DEXA scores [30]. We found that shorter men have lower hemoglobin than the taller men, which may be a marker of disease severity or longevity in this group. Anemia in CD is multifactorial, and for the most part is a result of micronutrient deficiency with chronic inflammation also playing a role [31]. IL-6, noted to be elevated in CD patients in its role potentially interfering with GH axis [25,26], is also involved in the pathogenesis of anemia of chronic inflammation [31]. Potentially, a subset of men have the most severe disease manifested as lower hemoglobin and height, and it is this group that drives down the average height of late-diagnosed CD men.

Sexual dimorphism in growth has been described in other chronic diseases such as Crohn's disease [32]. The mechanism, similarly, is not elucidated but the GH axis is known to be abnormal [33]. IBD patients are known to have hypogonadism [33] and sex steroids stimulate GH secretion. One theory is that sex discordance may be explained by testosterone playing a more pivotal role in GH secretion compared with estrogen [32]. Interestingly, a pattern of androgen resistance is also described in CD [34] – reversible with GFD.

Women in our study were significantly taller than the general population, but the absolute difference was small (3.1 cm) and statistical significance likely driven by the size of the comparison group. Interestingly, a 1991 study from Denmark also finds women to be slightly taller [8], but the vast majority of papers on height in CD find women to either be of similar height or slightly shorter [8–12].

The strengths of this study are that we analyzed measured variables (as opposed to self-reported) in a large cohort of patients, all examined and treated at one center. The patients were well matched demographically and temporally to the comparison group. One weakness of this study is incomplete information about some patients, leading to their exclusion. However, we do not believe this led to biased selection of shorter individuals – supported by the normal distribution of heights within our study group and sex discordance in the final result. And, the cohort is still quite large. Further epidemiologic survey is needed to corroborate these results, and additional investigation into

pathogenesis of CD-related short stature could help generate hypotheses of mechanisms. In addition, efforts should be made to increase the diagnosis of CD among men, a group that has an increased long-term mortality compared with young men without CD [35].

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Conflicts of interest

Benjamin Lebwohl is currently receiving a grant from the NIH (NIH KL2 KL2 RR024157). Peter Green has board membership on Alvine Pharmaceuticals and ImmusanT. For the remaining authors there are no conflicts of interest.

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