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ORIGINAL ARTICLE

Effect of gender on the manifestations of celiac disease: Evidence for greater malabsorption in men

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Abstract

Objective. Because celiac disease is a female-predominant disease we investigated the influence of gender on clinical manifestations of the disease in the United States. ***Material and methods***. Data were obtained on biopsy-proven adult patients with celiac disease from a database of patients seen between 1981 and 2001 in a University-based referral center. Z scores were calculated to adjust for age, ethnicity and gender using the National Health and Nutrition Examination Survey database as controls. ***Results***. The cohort consisted of 323 patients (211 F, 112 M). Men had a shorter duration of symptoms than women ($p=0.006$). There was no gender difference in the age at diagnosis or mode of presentation. Body mass index (BMI), mean hemoglobin and ferritin values were lower in women than in men, but the Z scores for these values were not significantly different, indicating that the differences are physiological. All lipid values were low (negative Z scores). Men had lower total cholesterol (162.0 ± 46.5mg/dl) compared to women (181.0 ± 40.0mg/dl), $p=0.02$ and lower Z scores (-1.10 ± 1.1) compared to women (-0.71 ± 0.9), $p=0.04$. Men had lower bone density T scores at the radius ($p=0.07$). Autoimmune diseases were present in 30.7% with a female to male ratio of 1:1, compared to the general population in which 3.2% have autoimmune diseases with a female predominance. ***Conclusions***. Most gender differences in celiac disease are physiological. However, men have indirect evidence of greater malabsorption than females and have female-predominant associated diseases when they present with celiac disease.

Key Words: *Autoimmune diseases, celiac disease, osteoporosis, sex*

Introduction

Celiac disease is an autoimmune enteropathy triggered by the ingestion of gluten in genetically predisposed individuals [1]. The disease is considered rare in the United States [2]; however, the incidence of the disease is increasing [3]. Serologic screening studies reveal the disease to be common in both the United States and the United Kingdom, approaching 1% of the population [4,5], indicating that there is a low rate of diagnosis. Celiac disease is a female-predominant disease with a female to male ratio of 2:1 or 3:1 [6,7]. In view of this female predominance, we sought to determine the influence of gender on the clinical manifestations of the disease in a large cohort of patients.

Material and methods

We reviewed the clinical data of all adult (age >16 years) celiac patients seen in a celiac disease center between 1981 and 2001. Only biopsy-proven patients, i.e. those who fulfilled strict criteria of small intestinal biopsy with total or partial villous atrophy and clinical or histologic response to a gluten-free diet, were included [8].

Clinical data had been entered into a database, retrospectively for those seen prior to 1990, and prospectively since then. Age at diagnosis, duration of symptoms prior to diagnosis, mode of presentation and family history of celiac disease were analyzed. In addition, we examined the following parameters at the time of diagnosis: body mass index

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(BMI), bone mineral density, serum cholesterol, hemoglobin and ferritin values. The prevalence of autoimmune diseases was assessed. Because triglyceride and ferritin values are not normally distributed, these data were summarized by medians and interquartile ranges while statistics were done after normalizing the data by logarithmic transformation. Z scores were calculated to adjust for age, ethnicity and sex, allowing comparisons between the genders. The National Health and Nutrition Examination Survey (NHANES) database was used as controls in Z-score calculations and T-score calculations for bone mineral density [9,10]. Autoimmune disease prevalence in the normal population was obtained from United States population-based studies [11]. The autoimmune diseases included in our analysis were: insulin-dependent diabetes, hypothyroidism, primary biliary cirrhosis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, Raynaud's phenomenon, Sjögren's syndrome, multiple sclerosis, peripheral neuropathy, psoriasis and alopecia areata. We did not include dermatitis herpetiformis because, while included in Ventura et al.'s study, it is not regarded uniformly as an autoimmune disease, but rather a cutaneous manifestation of celiac disease [12]. Since each autoimmune disease did not have a sufficient number of patients, we combined all autoimmune diseases in our final analysis.

Statistical analysis was performed using Student's t-test for continuous data and the χ^2 test for categorical (yes/no) data and proportions.

Results

A total of 323 patients (211 F, 112 M) fulfilled our inclusion criteria (Table I). There was no gender difference in age at diagnosis, number with family history of celiac disease, frequency of presentation with gastrointestinal symptoms, diagnosis made from screening those with a family history of celiac disease, or those who presented due to bone disease, anemia, or the incidental recognition of villous atrophy at endoscopy (Table I). Total villous atrophy was present in 46% of the women and 52% of the men. Women had a lower BMI compared to men, but when we examined the BMI Z scores there was no significant difference. Men had a shorter duration of symptoms than women ($p = 0.006$).

Mean hemoglobin and ferritin levels were lower in women, but there was no difference in the age- and gender-adjusted Z scores (Table II). Among the 110 patients (62 F, 48 M) in whom lipid values were available, total cholesterol, triglyceride, high-density lipoprotein (HDL) and low-density lipoprotein (LDL) values were all lower than those of age- and gender-matched controls using NHANES data (Table III), this is evidenced by negative Z scores for all lipid parameters (Table III). Total cholesterol was lower in men while other lipid values showed no gender difference. Because autoimmune disorders may contribute to lower cholesterol values, we examined cholesterol values in those patients without an associated autoimmune disorder and noted that the gender difference was maintained; females ($n = 47$), total cholesterol 176.85 ± 46.13 mg/dl, males ($n = 33$) total cholesterol 98.74 ± 45.42 mg/dl, $p < 0.0001$.

Bone densitometry was conducted in 168 patients (108 F, 60 M) at the time of diagnosis. The mean T scores for both men and women were indicative of osteopenia at the hip and lumbar spine, while men, but not women, had T-score values in the osteopenic range for the radius. Men had lower bone density, both T and Z scores, at the radius than women (Table IV).

Table I. Patient characteristics at diagnosis of celiac disease.

	Female (%) ($n = 211$)	Male (%) ($n = 112$)	p-value
Average age at diagnosis (years)	45.7 ± 15.1	47.8 ± 17.0	0.3
Reason for presentation and diagnosis			
Gastrointestinal symptoms	108 (51%)	55 (49%)	0.8
Screening family members	21 (10%)	17 (15%)	0.2
Bone disease	19 (9%)	7 (6%)	0.5
Anemia	19 (9%)	9 (8%)	0.9
Incidental endoscopy findings	16 (8%)	8 (7%)	0.9
Others	28 (13%)	16 (15%)	0.9
BMI	22.2 ± 4.6	24.0 ± 3.6	0.01
BMI Z scores	-0.8 ± 0.7	-0.7 ± 0.8	0.3
Positive family history	61 (29%)	31 (28%)	0.9
Number of patients with >5 years of symptoms at diagnosis	68 (33%)	19 (18%)	0.006

Table II. Hemoglobin and ferritin values at diagnosis of celiac disease.

	Hemoglobin (g/dl) & ferritin (ng/ml)					
	Female	Male		Z scores		
	($n=116$)	($n=77$)	p-value	Female	Male	p-value
Hemoglobin	12.2±1.5	14.2±1.5	<0.0001	−1.1±1.4	−0.9±1.3	0.3
Ferritin	23.0 (8–45)	80.5 (21–176)	<0.0001	−0.8±1.3	−0.8±1.6	0.8

The prevalence rate of autoimmune diseases was 30.7% (Table V). The overall autoimmune disease prevalence in the general population is considered to be 3.2% [11]. When we compared the autoimmune diseases identified in our study and in that of Jacobson et al. [11], insulin-dependent diabetes, hypothyroidism, primary biliary cirrhosis, systemic lupus erythematosus, rheumatoid arthritis, Sjögren's syndrome and multiple sclerosis had a prevalence rate of 2.8% in our cohort and 0.28% in the general population. Contrary to the general population, where autoimmune diseases predominate in females (female to male ratio of 2.7:1) [11], the gender ratio was 1:1 in our celiac disease cohort with 30.3% of females and 31.3% of males having autoimmune diseases.

Discussion

While celiac disease is a female-predominant disease, our study demonstrated that men had a shorter duration of illness before diagnosis and more severe manifestations of malabsorption. There were no gender differences in age at diagnosis, mode of presentation, prevalence of gastrointestinal symptoms or family history of celiac disease.

In an Italian study, Ciacci et al. [6] demonstrated that women had an earlier age at diagnosis, more symptoms, lower body weight and more severe anemia. They, however, did not examine Z scores. In our study both men and women with celiac

Table IV. Bone density (T and Z scores) at the time of diagnosis of celiac disease.

	Female ($n=108$)	Male ($n=60$)	p-value
T scores			
Lumbar	−1.3±1.2	−1.1±1.6	0.4
Hip	−1.4±1.1	−1.2±1.3	0.3
Radius	−0.9±1.5	−1.5±1.6	0.07
Z scores			
Lumbar	−0.6±1.2	−0.8±1.6	0.4
Hip	−0.8±1.0	−0.7±1.1	0.5
Radius	−0.3±1.3	−0.8±1.5	0.05

Table V. Prevalence of autoimmune diseases in celiac patients.

	Female	Male	Both genders
Insulin-dependent diabetes mellitus	8	1	9
Hypothyroidism	24	12	36
Primary biliary cirrhosis	2	1	3
Autoimmune hepatitis	1	1	2
Systemic lupus erythematosus	2	2	4
Rheumatoid arthritis	1	3	4
Raynaud's phenomenon	11	3	14
Sjögren's syndrome	3	1	4
Multiple sclerosis	1	3	4
Peripheral neuropathy	7	6	13
Alopecia areata	1	0	1
Psoriasis	3	2	5
Total	64	35	99

Table III. Serum lipid values at diagnosis of celiac disease.

	Plasma levels (mg/dl)					
	Female	Male		Z scores		
	($n=62$)	($n=48$)	p-value	Female	Male	p-value
Total cholesterol	181.0±40.0	162.0±46.5	0.02	−0.71±0.9	−1.10±1.1	0.04
Triglycerides	88.0±56.0	96.5±52.0	0.4	−0.61±1.0	−0.67±0.9	0.8
HDL	50.2±16.8	41.3±16.7	0.02	−0.24±1.1	−0.27± 1.3	0.9
LDL	110.2±29.0	111.3±42.7	0.9	−0.50±0.8	−0.59±1.2	0.7

Abbreviations: HDL = high-density lipoprotein; LDL = low-density lipoprotein.

disease had lower BMI than age- and gender-matched populations, as reflected by the negative Z scores. However, there was no difference between the Z scores of men and women, indicating that the gender differences were physiological, and not due to celiac disease. This is because the Z scores normalize for age and gender, allowing comparisons between genders; the gender differences in absolute BMI therefore reflect natural physiological differences.

Iron-deficiency anemia is a common problem for patients with celiac disease [13] and women have more severe anemia and lower iron stores than men [6]. However, in our cohort both women and men had lower values for hemoglobin and ferritin than age- and gender-matched controls, without a significant difference between the Z scores, indicating that the gender differences in hemoglobin and ferritin are physiological.

Cholesterol is absorbed in proximal intestine, the site of villous atrophy in celiac disease. It is therefore not surprising that celiac disease patients have lower serum cholesterol and higher fecal neutral steroid excretion consistent with malabsorption of cholesterol [14–16]. The negative Z scores for total cholesterol, LDL, HDL and triglycerides, for both men and women in our study confirm that patients with celiac disease have malabsorption of cholesterol and as a result have lower lipid values than the general population. More importantly, men had lower total cholesterol than women, which is opposite from that in the general population. This is indirect evidence of greater malabsorption in men. The low cholesterol supports the unconfirmed concept that celiac disease may be protective against cardiovascular disease [5,17]. The values we have reported are those at diagnosis. It is our experience that the parameters of malabsorption are corrected with a gluten-free diet, though this has not been systematically analyzed.

Reduced bone density is common in celiac disease [18] and thought to be multifactorial in etiology, with calcium malabsorption and resultant secondary hyperparathyroidism considered to be the major factor [19]. In our study, all patients, both men and women, had osteopenia at two sites, while the only gender difference was lower T and Z scores in the radius in men compared to women. This provides indirect evidence of greater malabsorption in men.

Celiac disease represents a model of food-dependent autoimmunity in which patients frequently have other autoimmune diseases [12,20–23] and there is a considerable body of evidence to suggest that the presence of celiac disease is a factor in the development of these other autoimmune diseases [1,12,24]. We found a prevalence of autoimmune diseases among adults with celiac disease (30.7%) similar to that found in the Italian study by Ventura et al. [12] in which 34% of patients (age >20 years) had an autoimmune disease. These figures are 10-fold higher than the prevalence in the general population [11]. When we compared the seven autoimmune diseases used in both our study and Jacobson's study [11], the prevalence rate was still 10 times higher in our cohort of patients with celiac disease (2.8% versus 0.28%). Again, this clearly demonstrates that patients with celiac disease are at an increased risk of developing other autoimmune diseases. Further supporting evidence of a causal link between celiac disease and the development of autoimmune diseases lies in the fact that, in children, organ-specific autoantibodies disappear on a gluten-free diet [24].

Autoimmune diseases usually have a female predominance with a female to male ratio of 2.7:1 [11]. This gender difference was lost in celiac disease as men had equal propensity to develop autoimmune diseases as women. This implies that men who have celiac disease are at much higher risk than men who do not have the disease to develop autoimmune diseases. The reason for this is not clear.

We found significant gender differences in patients with celiac disease. Men had a shorter duration of symptoms and indirect evidence of a greater degree of malabsorption as manifested by lower total serum cholesterol and poorer bone density. They also tended to develop female-predominant diseases at the same rate and severity as women such as iron-deficiency anemia and autoimmune diseases. The reason for this is not clear, but may be related to hormonal changes that occur in men with celiac disease [25,26]. There may be the question of under-reporting of symptoms in women, or a higher rate of atypical disease that leads to later diagnosis. There is also concern that there may be a more rapid progression of the disease in men. Despite the fact that celiac disease is a female-predominant disease, men had more severe manifestations of the disease.

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