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Optimal age for screening lumbar osteoporosis in celiac disease

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Osteoporosis is a common and important predictor of poor outcomes in celiac disease (CD), which puts many patients at risk of further fractures. Our objective was to evaluate the stratification of osteoporosis odds in CD patients based on their age, aiming to determine the optimal timing for initiating osteoporosis screening in this population.This cross-sectional study was performed on adult CD patients who were referred to the Celiac Clinic Center between 2015 and 2020. The exclusion criteria included individuals with endocrine disorders, corticosteroid use, smoking habit, post-menopausal women, and patients younger than 25 years old. Intestinal pathology, bone mineral density (BMD), TGA-IgA serum level, and serum vitamin D were assessed at the time of diagnosis. A total of 199 CD patients, who underwent lumbar densitometry at the time of their diagnosis, were included in the study with a mean age of 39.14 ± 8.99 years old. Osteoporosis was observed in 23.6% patients, of whom 25.5% were men and 74.5% were women. The results revealed a notable disparity across the four age groups. After accounting for potential confounding factors in multivariate analysis in fully adjusted model, our findings demonstrated that individuals between the ages of 45 and 55 had 22% higher odds of developing lumbar osteoporosis (odds ratio, 1.22; 95% CI, 1.02–1.45) compared to those aged 25–35. Individuals with CD are at an increased risk of developing lumbar osteoporosis in middle age. Therefore, it is recommended to begin BMD screening at age 45 and beyond. This recommendation further emphasizes the importance of receiving appropriate treatment to prevent fractures and preserve bone health.

Keywords Celiac disease, Bone mineral density, Osteoporosis, BMD, Age

Abbreviations

BMD	Bone mineral density
BMI	Body mass index
CD	Celiac disease
CI	Confidence Interval
NOF	National Osteoporosis Foundation
OPG	Osteoprotegerin
PTH	Parathyroid hormone
RANKL	Receptor activator of nuclear kappa-B ligand
TBS	Trabecular bone score
T2DM	Type 2 diabetes mellitus
WHO	World Health Organization
y/o	Years old

Celiac disease (CD), as a chronic immune-based enteropathy, occurs in genetically-predisposed individuals triggered by dietary gluten. Notably, CD has a wide range of intestinal and extra intestinal manifestations such as malabsorption, weight loss, steatorrhea, anemia, musculoskeletal and growth problems, and infertility[1–3]. Osteoporosis is known as a prevalent and an important predictor of poor outcomes in CD, which puts many patients at the risk of further fractures. We have recently witnessed that the bone loss is becoming more prevalent in CD even by excluding menopausal women who are considered as the most important confounding factor[3].

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According to a recent systematic review, a significant percentage of young women between the ages of 20 and 35 who are newly diagnosed with CD are susceptible to having lower bone mineral density (BMD). Additionally, the analysis found that 18–35% of celiac patients have osteoporosis, indicating that bone abnormalities are quite common in CD[4]. The onset of bone loss begins at the age of 35, but it reaches its highest point during late middle age (around 50 years) and predominantly affects women[5]. Consequently, it is important to evaluate BMD in young women at the time of CD diagnosis. However, it remains uncertain whether these findings can be extended to young men[4]. The risk of fractures would increase among patients with osteoporosis, which could consequently have a detrimental effect on quality of their lives[6]. It has been reported that CD patients are 40% more susceptible to developing fracture's risk compared to age-matched control subjects[7]. It is of utmost importance to identify celiac disease patients who are at an increased risk of experiencing osteoporotic fractures. This identification is crucial in order to provide them with tailored and comprehensive care, which may include the consideration of pharmacological treatment options[8]. This study aimed to stratify the odds of osteoporosis based on the patient's age to determine the optimal time to initiate osteoporosis screening in individuals with CD.

Methods

Study design

The current study was conducted on patients referred to the Celiac Disease Center during 2015–2020. BMD was measured using DXA, and spinal BMD was evaluated at the time of CD diagnosis and before starting a gluten-free diet for the patients. According to the World Health Organization (WHO) criteria, bone loss was defined based on the T score. However, the 2019 ISCD PDC recommends the use of the Z score in females prior to menopause and in males younger than age 50, as preferred over the T score. Z-score of -2.0 or lower is defined as "below the expected range for age" and a Z-score above − 2.0 is "within the expected range for age and are normal." and for men older than 50 T score are preferred. In our study for patients aged between 25 and 50 years old, we evaluated Z score and for men older than 50 we evaluated T score. Based on Larijani et al., peak bone mass in the Iranian population was found to be comparable to that of Western countries, occurring around 21–24 years old, and decreasing after the age of 50[9]. In addition, the study population was divided into four groups as follows: group 1 = 25–35 years old (y/o), group 2 = 35–45 y/o, group 3 = 45–55 y/o, and group 4 = 55–70 y/o.

Sample size and selection criteria

In the present study, 199 celiac patients who diagnosed based on pathology and serology were enrolled. The modified Marsh classification was used for the classification of mucosal lesions[10]. TGA-IgA Kit (by Euroimmun, Germany) used to assess the levels of anti-tissue transglutaminase antibody IgA (TGA-IgA). Correspondingly, the cases with a positive TGA-IgA level and pathologic changes of Marsh grade ≥ 2 were considered as CD. Moreover, symptomatic patients with a Marsh grade 1, but a high titer of TGA-IgA[11], or positive DQ2-DQ8, were considered as CD as well. Afterward, premenopausal women and men aged more than 25 years old were included, with exclusion criteria of any medical disease's history, pregnant women, menopausal women, individuals taking drugs (including steroids, anticonvulsants, anticoagulants, and calcium supplements), patients with other certain diseases (such as chronic liver disease, chronic kidney disease, thyrotoxicosis, hypogonadism, and other malabsorptive disorders), and alcohol abusers (≥ 3 drinks/day) as the confounding factors for bone loss. Patients referred for bone densitometry using DXA (OSTEOCORE 3 Visio). All methods were performed in accordance with the relevant guidelines and regulations of the Declaration of Helsinki.

Statistical analysis

Excel software was applied for data entry and management. All statistical analyses were performed on Stata11.0 (StataCorp, Texas, US). A p-value less than 5% was considered as significant level for all statistical tests. Central indices of mean ± SD or median with interquartile range were employed for continuous variables and frequency (percentage) for categorical/ qualitative variables. Between groups comparisons were performed using the chi-square test, independent samples t-test or Mann–Whitney U-test to evaluate the differences in demographic, clinical, and laboratory variables, between subjects with lumbar osteoporosis vs. without lumbar osteoporosis. Univariate and multivariable binary logistic regression analyses were performed to comprehensively assess the association of demographic, and laboratory data with osteoporosis status. All covariates that were either statistically significant in univariate examinations (P-Value < 0.25) or that were chosen based on previous studies and existing knowledge were included in multivariable model. Adjusted odds ratios with 95% Confidence Interval (CI) were presented for potential determinant factors of lumbar osteoporosis. Moreover, the area under the ROC curve (AUC) curve analysis was performed to determine the optimal age for screening lumbar osteoporosis in CD.

Results

Characteristics of the study participants

In this study, we enrolled 199 adult CD patients who had lumbar densitometry at the time of their diagnosis, including 55 men (27.6%), and 144 women (72.4%) with a mean age of 39.14 ± 8.99 years old (Fig. 1). Osteoporosis was observed in 23.6% patients, of whom 25.5% were men and 74.5% were women. There was a significant difference among the four decades of life (age groups) (P = 0.02). Moreover, the clinical characteristics of the study population revealed no significant difference in body mass index (BMI) between osteoporotic and non-osteoporotic patients, even after further stratification of BMI into categories of healthy weight, overweight, and obesity (Table 1). However, we could not find any significant relationship between sex, TGA-IgA, parathyroid hormone (PTH) level, and Type 2 diabetes mellitus (T2DM) in patients with osteoporosis compared to no

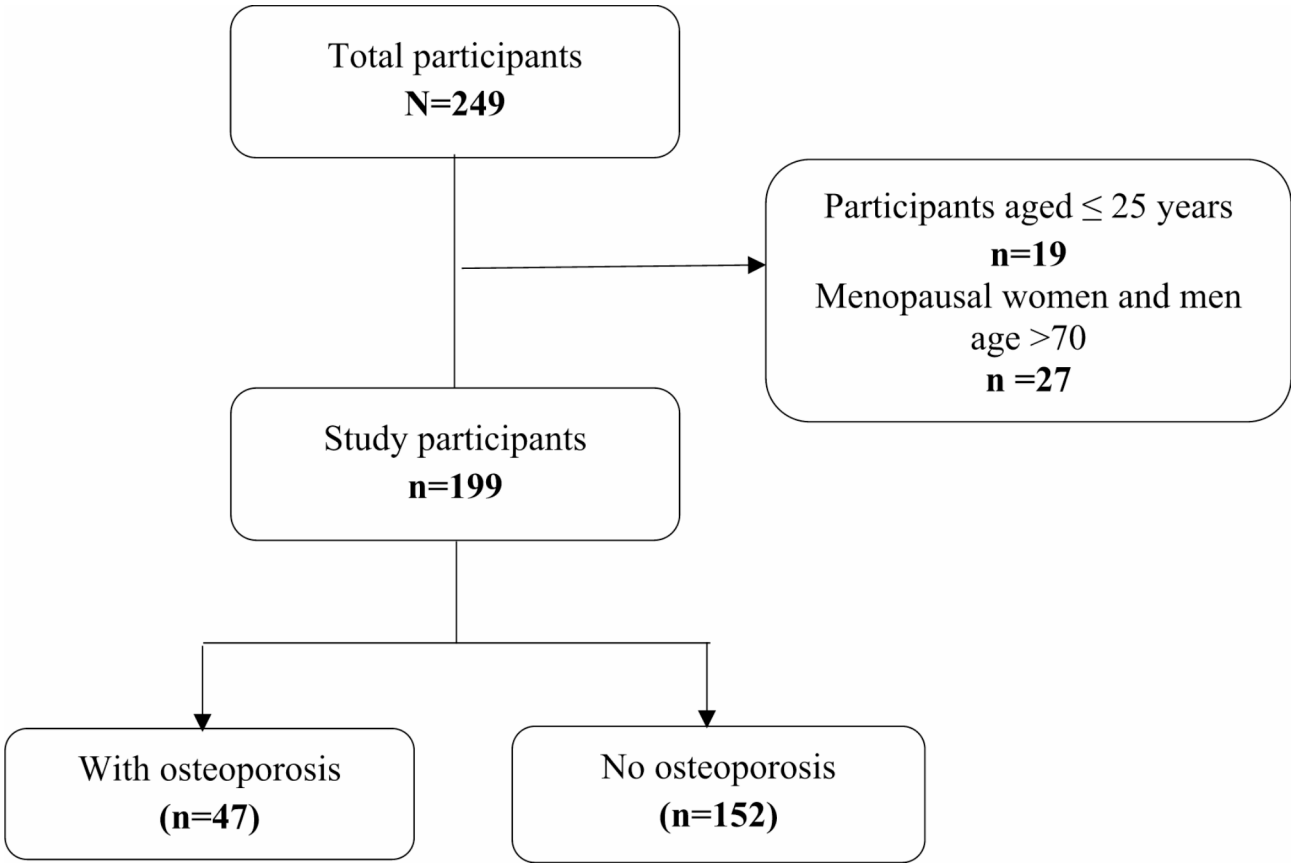

Fig. 1. Flow chart of participants selection.

osteoporotic participants. The majority of the patients had Marsh III of pathology and no significant correlation was found between Marsh grading and lumbar osteoporosis ($P=0.09$). Additionally, among the CD patients with osteoporosis, 43.80% had normal levels of 25(OH) D, 28.10% had low levels, and 28.10% had insufficient levels. Furthermore, no significant correlation was discovered in the 25(OH) D level between individuals with lumbar osteoporosis and those without osteoporosis. ($P=0.98$) (Table 1).

Age-related changes in the prevalence of osteoporosis

In further analysis, we classified the entire population into four age groups. Table 2 illustrates the raw data and also three models of multivariate-adjusted risk of osteoporosis stratified by age categories. Our analysis demonstrates that individuals in the 45 to 55-year-old age range have significantly increased risk of developing osteoporosis. The likelihood of osteoporosis was found to be higher in participants aged 45–55 compared to those in the 25–35 age group (odds ratio, 1.20; 95% CI, 1.04–1.39). Furthermore, even after adjusting for potential confounders such as sex, smoking, mucosal atrophy (Marsh), BMI, and T2DM, this association remained significant (odds ratio, 1.22; 95% CI, 1.02–1.45). In addition, in the univariate model, the odds of osteoporosis in the group aged over 55 years old were estimated to be 1.95 (95% CI, 1.02–2.26), although no significant association was found in a fully adjusted model (1.09 (95% CI, 0,92-1.29)) (Table 2). Additionally, there was no significant association between sex, BMI, and T2DM and the possibility of osteoporosis, in both univariate and multivariable models. When assessing the pathological spectrum, it was observed that patients with Marsh III had a 20% higher odds of having osteoporosis compared to those with Marsh I. However, it is important to note that this association did not reach statistical significance. Based on the ROC curve analysis for predicting osteoporosis in CD patients aged 45–55, the AUC of 0.65 (95% CI, 0.56–0.75) ($P=0.002$) was reported (Fig. 2).

Discussion

Using data from Celiac Disease Center, we showed that after adjusting for potential confounders, the odds of lumbar osteoporosis in patients aged between 45 and 55 years old were 22% higher than those in the 25–35 years old. Interestingly, we observed that none of the potential risk factors, including sex, grade of mucosal atrophy (Marsh), BMI, and T2DM, were statistically linked to the odds of osteoporosis in our study. However, a notable finding was the positive association between patients aged 45 to 55 years old and the odds of developing osteoporosis. Remarkably, even after considering potential confounders, the association remained significant.

Osteoporosis is a common, but underappreciated disease, which is more frequently recognized as an important predictor of poor outcomes in CD, and puts many patients at further fractures' risk. Lumbar spine

Variables	With osteoporosis ($n=47$)	No osteoporosis ($n=152$)	*P*-Value
Calcium, Mean ± SD	8.98 ± 1.00	9.26 ± 0.53	0.05
Phosphate, Mean ± SD	3.64 ± 0.56	3.72 ± 0.61	0.55
Age, year, n (%)	37.99 (8.57)	42.87 (9.40)	< 0.001
25-34.9	12 (25.50)	63 (41.40)	0.02
35-44.9	13 (27.70)	51 (33.60)	
45-54.9	19 (40.40)	36 (23.70)	
55–70	3 (6.40)	2 (1.30)	
BMI, Mean ± SD	22.09 ± 4.31	23.44 ± 4.83	0.13
< 18.5 kg/m2	5 (13.90)	17 (13.70)	0.74
18.5–24.9	23 (63.90)	67 (54.00)	
25-29.9	6 (16.70)	27(21.80)	
≥ 30	2 (5.60)	13 (10.50)	
Female, n (%)			
Male	12 (25.50)	43 (28.30)	0.71
Female	35 (74.50)	109 (71.70)	
Marital Status, n (%)			
Single	11 (23.40)	16 (11.00)	0.03
Married	36 (76.60)	130 (89.00)	
Smoking, n (%)			
Smoker	7 (17.90)	7 (5.40)	0.02
No smoking	32 (82.10)	122 (94.60)	
25(OH) D Level, n (%)			
Optimal vit. D level	14 (43.80)	40 (42.10)	
Sub-optimal vit. D level	9 (28.10)	28 (29.50)	0.98
Vit D deficiency	9 (28.10)	27 (28.40)	
Mucosal atrophy, n (%)			
Marsh I	2 (4.30)	13 (8.60)	
Marsh II	1 (2.10)	17 (11.20)	0.09
Marsh III	44 (93.60)	122 (80.30)	
TTG-IgA titer (times ULN)			
< 3	2 (4.30)	17 (11.40)	
3–10	5 (10.90)	34 (22.80)	0.05
≥ 10	39 (84.80)	98 (65.80)	
PTH Level, n (%)			
Low	1 (5.90)	1 (1.90)	
Normal	9 (47.10)	37 (71.20)	0.15
High	8 (47.10)	14 (26.90)	
T2DM, n (%)			
Yes	1 (2.20)	10 (6.70)	0.46
No	44 (97.80)	140 (93.30)	

Table 1. Demographic and clinical characteristics of study population (CD patients with and without osteoporosis). ALP, alkaline phosphatase; BMI, body mass index; 25(OH) D, 25-hydroxyvitamin D; TTG-IgA, tissue transglutaminase IgA (times upper limit normal), PTH, Parathyroid hormone; T2DM, Type 2 diabetes mellitus.

BMD testing using the National Osteoporosis Foundation (NOF) guidelines, is essential to diagnose lumbar osteoporosis cases that helps clinicians for either treatment or vertebral fracture prevention[12,13]. In the USA, the prevalence rate of osteoporosis in the population aged between 50 and 59 years old has been reported at 5.1%, including 6.8% women and 4.3% men. Moreover, in the population aged between 60 and 69 years old, it was 3.3% among male cases[14]. In a meta-analysis focusing on osteoporosis prevalence in 2119 Iranian participants, the research revealed a notable increase in osteoporosis rates among individuals aged more than 50 y/o, with females showing a higher prevalence of 29% osteoporosis compare to 16% in men[15]. Similarly, in our study, the prevalence of osteoporosis in men over 50 years old was reported as 16.4%.

In the current study, we have attempted to describe the optimal patients' age for evaluating the odds of osteoporosis among CD patients. Totally, our results indicated a prevalence rate of 27% for osteoporosis, demonstrating a higher spread rate compared to their counterparts in the general population, where a prevalence

Variables	Crude		Model 1		Model 2		Model 3	
Age, year	OR (95% CI)	*P*-Value	OR (95% CI)	*P*-Value	OR (95% CI)	*P*-Value	OR (95% CI)	*P*-Value
25-34.99	1 (reference)		1 (reference)		1 (reference)		1 (reference)	
35-44.99	1.04 (0.91–1.19)	0.54	1.04 (0.91–1.19)	0.01	1.06 (0.91–1.23)	0.58	1.01 (0.92–1.29)	0.32
45-54.99	1.20 (1.04–1.39)	0.01	1.20 (1.04–1.39)	0.01	1.14 (0.98–1.34)	0.02	1.22 (1.02–1.45)	0.03
≥ 55	1.955 (1.02–2.26)	< 0.02	1.61 (1.17–2.37)	0.57	1.51 (1.02–2.26)	< 0.001	1.09 (0.92–1.29)	0.16
Sex								
Male	1 (reference)	0.71	1 (reference)		1 (reference)		1 (reference)	0.62
Female	1.02 (0.89–1.170)		1.06 (0.92–1.21)	0.41	1.04 (0.90–1.20)	0.59	1.04 (0.89–1.21)	
Smoking								
No	1 (reference)	0.01			1 (reference)		1 (reference)	
Yes	1.34 (1.07–1.68)				1.24 (0.97–1.57)	0.08	1.10 (0.85–1.41)	0.46
Pathology								
Marsh I	1				1 (reference)		1 (reference)	
Marsh II	0.92 (0.69–1.23)	0.60			0.86 (0.64–1.15)	0.59	1.04 (0.73–1.46)	0.85
Marsh III	1.14 (0.91–1.42)	0.24			1.07 (0.84–1.34)	0.31	1.20 (0.90–1.58)	0.21
BMI, Mean ± SD								
< 18.5 kg/m2	1 (reference)						1 (reference)	
18.5–24.9	1.03 (0.85–1.25)	0.77					1.07 (0.86–1.33)	0.54
25–29.9	0.96 (0.76–1.20)	0.69					0.94 (0.72–1.22)	0.65
≥ 30	0.91 (0.69–1.20)	0.50					0.92 (0.67–1.25)	0.59
T2DM								
No	1 (reference)	0.25					1 (reference)	0.65
Yes	0.86 (0.67–1.11)						0.92 (0.63–1.33)	

Table 2. Multivariable-adjusted risk of osteoporosis stratified by age categories (study population, $n = 199$; people with osteoporosis, $n = 47$). Model 1: adjusted for sex Model 2: adjusted for sex, smoking, and pathology Model 3: adjusted for sex, smoking, pathology, BMI, and T2DM

rate of 17% has been observed[16]. In our previous results, the prevalence of 14.4% for osteoporosis and 39.6% for osteopenia were determined by conducting a systematic review recruiting 563 premenopausal women and men with CD[3].

Another systematic review on 188 patients revealed that newly diagnosed young adults even in 20–35 years old with CD possessed reduced BMD, as compared to healthy individuals. They also concluded that CD patients at the range of 20–35 years old are at greater odds of having decreased BMD, especially young women, and should be evaluated during diagnosis. There is insufficient compelling evidence to support the efficacy of nutritional supplements or antiresorptive therapies in preventing bone fractures at this age[4].

In a study by Galli et al. in 2018, 60% of CD patients were found to have decreased BMD with 17.8% osteoporosis and 42.5% osteopenia. As indicated by their analysis, low weight, male gender, and CD patients with age above 45 years, were at high risk of osteoporosis[17]. Ageing and menopause are two major risk factors for bone loss, while low BMD was reported more commonly even among premenopausal women compared to controls[18].

Metabolic bone disease is a common extra-intestinal manifestation of CD, along with several other autoimmune and inflammatory conditions. Chronic inflammation and malabsorption of nutrients in CD can lead to a reduction in bone density and an elevated risk of fractures, especially in the spine, hip, and wrist[19]. There are different theories proposed for the pathophysiology of bone loss in CD[6,7,20]. These may include chronic inflammation and reduced absorption of nutrients including calcium and vitamin D[21] which cause secondary hyperparathyroidism and in turn lead to elevate skeletal resorption, loss of bone density and increased risk of fractures[22]. Hyperparathyroidism also is common among CD adult patients (27%), who were newly diagnosed before GFD, and also among children (between 12% and 54%)[23,24]. However, in our study, no significant correlation was found in the levels of vitamin 25(OH) D, and osteoporosis. Moreover, there was no significant correlation between, the concentration of TGA-IgA, as well as grade of mucosal atrophy (Marsh) in osteoporotic celiac patients compared to patients without osteoporosis. In contrast, another study has previously reported a correlation between high levels of TGA-IgA and low BMD[25]. Pro-inflammatory cytokines can also alter the ratio of important regulators of bone remodeling including osteoprotegerin (OPG) and receptor activator of nuclear kappa-B ligand (RANKL), which can specifically enhance production of RANKL and reduce production of OPG, resulting in an increased ratio of RANKL/OPG and promote osteoclastogenesis[26]. Moreover, a decreased function of the gonads can also contribute to the bone loss[27]. Finally, other proposed mechanism for bone disease in CD is related to the low weight and inadequate nutrient intake. Furthermore, low weight and malnutrition may lead to hormonal imbalances that can further increase the risk of bone loss. Several studies have shown that by eliminating gluten from the diet, individuals with CD can absorb calcium and vitamin D more effectively,

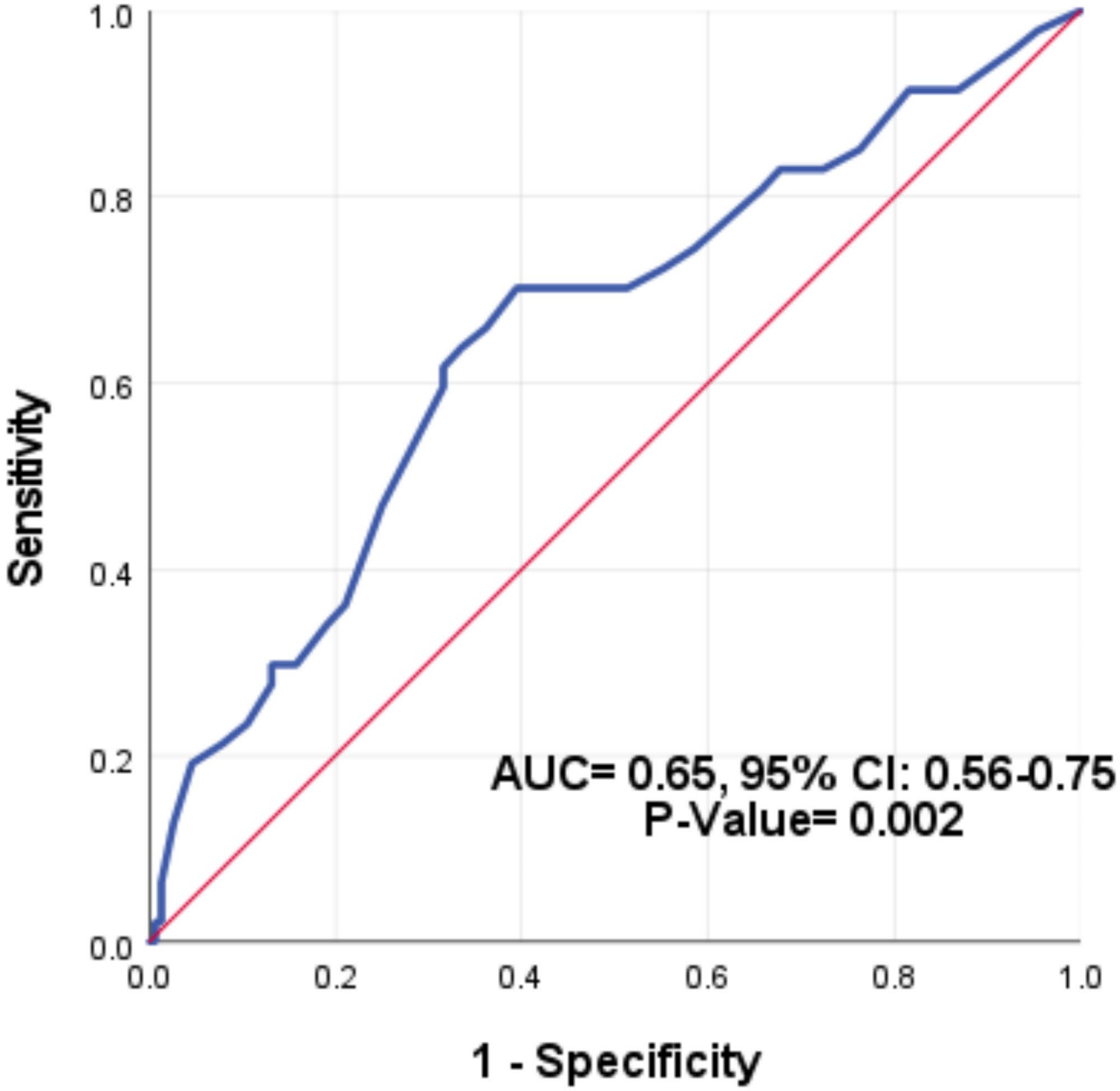

Fig. 2. ROC curve for predicting osteoporosis in CD patients aged 45–55. The ROC AUC was shown in the figure. ROC, receiver operating characteristic; AUC, area under the ROC curve; CI, confidence interval.

which can lead to improvements in BMD over time[28]. Additionally, some studies have suggested that gluten itself may imply a negative influence on bone health, so a gluten-free diet could provide further benefits for patients with CD. However, it is possible for CD patients to still have a lower BMD and higher risk of fractures compared to others[29].

There is currently no consistence on the timing of dual-energy x-ray absorptiometry (DEXA) evaluation in CD patients. Various guidelines recommend assessing BMD screening in patients with CD. However, the optimal age for screening remains uncertain at present. The main objective of this study was to categorize the odds of osteoporosis according to patients' age, with the aim of determining the optimal timing for initiating osteoporosis screening in individuals with CD.

The first limitation of our study was the lack of trabecular bone score (TBS) in the BMD report, which could have offered a more comprehensive assessment of bone loss. Additionally, due to the cross-sectional design of our study, establishing temporal or causal relationships between age groups and osteoporosis in celiac patients was not feasible. Therefore, it is essential for future prospective, large-scale, multicenter studies to investigate the association between age groups and osteoporosis in order to validate these findings. This research sought to assist physicians in improving the management of osteoporosis in CD patients. Prior to any complication

resulted from bone loss, we should conduct a systematic approach for screening, in order to optimize the bone quality.

Conclusions

Patients with CD should be monitored for possible bone disease and may need to undergo bone densitometry and receive appropriate treatment to prevent fractures and maintain bone health. Our results indicated that after adjusting for potential confounding factors, the odds of lumbar osteoporosis in celiac patients aged between 45 and 55 years old were 22% higher than those in the 25–35 years old. Celiac patients are susceptible to lumbar osteoporosis in their middle ages, so it is recommended to screen BMD from the age of 45 years old.

Data availability

The datasets analyzed during the current study are available from the corresponding author at reasonable request.

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Author contributions

A.G. and R.G. formulated the research question and designed the study; M.S. and V.Gh. performed the statistical analysis; A.G., R.G., and S.S. conducted the data interpretation and discussion; S.S. and N.B. drafted the manuscript. All authors read and approved the final manuscript.

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Declarations

Competing interests

The authors declare no competing interests.

Ethics approval and consent to participate

Study protocols and consent forms were approved by the ethics committee of Mashhad University of Medical Sciences with approval code IRMUMSREC.1396.112. All participants provided informed consent to participate in the study.

Additional information

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