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ORIGINAL ARTICLE

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# Serological screening for celiac disease in premenopausal women with idiopathic osteoporosis

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**Abstract** The aim of this study was to perform serological testing to screen for celiac disease (CD) among premenopausal women with idiopathic osteoporosis and to investigate the bone turnover in patients who are seropositive for CD. We studied 89 premenopausal women with idiopathic osteoporosis. The serological screening protocol was based on a two-level evaluation. The first level consisted of determining serum level of IgA antigliadin antibodies (AGA). Subjects who were negative for IgA AGA were classified as not having CD, while samples testing positive for IgA AGA underwent a second level of the screening process. For the second level of screening, the serum IgA endomysial antibody (EMA) test was performed. Bone metabolism was evaluated by serum calcium (Ca), phosphorus, alkaline phosphatase, parathyroid hormone (PTH), 25 (OH) vitamin D, osteocalcin (OC), urinary deoxypyridinoline (dPD), and 24-h urinary calcium levels. Of the 89 patients evaluated, 17 were found to have positive IgA AGA tests (19%) and 9 were found to be positive for EMA (10.11%). EMA-positive patients showed lower values of serum Ca ($p < 0.05$) and 25 (OH) vitamin D ($p < 0.01$) and significantly higher values of PTH ($p < 0.01$) compared with the EMA-negative patients. The level of urinary dPD was found to be significantly higher in EMA-positive patients ($p < 0.05$). The results of this study suggest that all patients with idiopathic osteoporosis should be screened for CD by measurement of EMA. Additionally, we believe that serological screening for CD and detection of such patients will allow determination of the most convenient treatment strategies for osteoporosis.

**Keywords** Antiendomysial antibodies · Celiac disease · Idiopathic osteoporosis

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## Introduction

Osteoporosis is a disease characterized by low bone mass, microarchitectural deterioration of bone tissue, and consequent skeletal fragility associated with an increase in fracture risk [1], whereas the term "idiopathic osteoporosis" defines the occurrence of osteoporosis in premenopausal women or men under the age of 60 who do not have an obvious secondary cause [2].

Celiac disease (CD) is an inflammatory condition of the gastrointestinal tract affecting the small intestine caused by exposure to dietary gluten in genetically predisposed individuals and additionally one of the important causes of the intestinal malabsorption [3]. In addition, CD also has extraintestinal effects, namely, osteopenic bone disease, neurogenic symptoms, and infertility [4–7]. Adult people may have subclinical and silent forms of CD [8–11]. Osteopenia or osteoporosis are well-known consequences of CD [12]. Interestingly, bone loss might be the early or preceding symptom of CD, and bone mineral density may be even lower in clinically silent cases than in symptomatic celiac patients [13–15]. In patients with idiopathic osteoporosis, subclinical CD unusually appears to be increased. A previous study reported that prevalence of CD is higher among idiopathic osteoporosis patients than in the general population [16]. As a result of the wide clinical spectrum and potential complications of this disease, highly sensitive and specific noninvasive screening methods have been developed to identify and treat new patients defined as "subclinical or silent." According to the findings mentioned above, it is

suggested to screen for CD routinely in patients with osteoporosis [15].

Four types of serological tests are used to diagnose CD: IgA endomysial antibodies (EMA), IgA transglutaminase antibodies (TG-ab), IgA antigliadin antibodies (AGA), and IgG AGA. These tests were found to be highly sensitive and specific for CD [17].

The aim of this study was to perform serological testing to screen for CD among premenopausal women with idiopathic osteoporosis and to investigate the bone turnover in patients who are seropositive for CD.

## Materials and methods

### Subjects

The study was carried out at Osmangazi University, Faculty of Medicine Hospital. We studied 89 premenopausal patients with idiopathic osteoporosis classified according to the WHO criteria as having bone mineral density (BMD) measured at the lumbar spine (L1–L4) ≥2.5 SD below the young adult mean. The subjects' mean age was 35.96 years (range: 25–44 years).

The main inclusion criteria included idiopathic low bone mineral density, premenopausal status, and normal values of serum calcium, phosphorus, alkaline phosphatase, and creatinine. Exclusion criteria were diseases well known to affect bone metabolism (Cushing's, hyperthyroidism, hyperparathyroidism, renal disease, underlying malignancy, liver disease, osteogenesis imperfecta, acromegaly, or ethanol abuse), any medication known to affect bone turnover such as glucocorticoids, and diseases known to associate with CD (dermatitis herpetiformis, insulin-dependent diabetes mellitus, autoimmune thyroid diseases, systemic lupus erythematosus, Sjögren's syndrome, polymyositis, autoimmune hepatitis, sclerosing cholangitis, primary biliary cirrhosis, IgA nephropathy, interstitial lung disease including chronic fibrosing alveolitis, idiopathic pulmonary hemosiderosis, and Down syndrome). Additionally, patients with IgA deficiency were not included to prevent invalidation of the specific serological tests. Patients were also excluded from study for any of the following reasons: if they had taken calcium supplementation >1500 mg/day, vitamin D supplementation >800 IU/day, anabolic steroids, parathyroid hormone, calcitonin, estrogen, androgens, or bisphosphonates within the 12 months previous to study entry.

For the control group, 76 premenopausal healthy women without osteoporosis as confirmed by the dual-energy X-ray absorptiometry (DXA) technique were selected. The mean age of the controls was 34.95 years (range: 25–45 years) and the mean body mass index (BMI) was 25.52 kg/m$^2$ (range: 19.17–32.03).

All patients were questioned regarding bowel symptoms, personal and family history of CD, or other systemic disease, and a detailed systemic clinical examination was performed. None of the patients had symptoms of CD such as malabsorption, diarrhea, weight loss, or anemia. The Ethics Committee of the Osmangazi University Medical School approved this study and all patients gave their written consent.

### BMD measurements

The standardized BMD measurements in the femoral neck and lumbar spine (L1–L4, anteroposterior) were performed by DXA (Hologic QDR, 4500, Hologic, Inc., Bedford, Mass., USA). BMD was expressed as standard deviation scores, which compare individual BMD determinations to those of young (T) and age/sex-matched (Z) normal populations. The *t* and *z* scores used in this study were the population-specific reference values [18].

### Biochemical measurements

Serum calcium, phosphorus, alkaline phosphatase, aspartate transaminase, alanine transaminase, gamma-glutamyl transaminase, creatinine, glucose, total protein, albumin, bilirubin, cholesterol, cortisol, tumor markers, free T3, T4, and thyroid-stimulating hormone levels were measured in venous blood using routine clinical laboratory methods. Serum calcium was corrected for albumin concentration. Serum intact parathyroid hormone (PTH) was measured using electrochemiluminescence immunoassay with the original kit (Modular Analytics E170, Roche Diagnostics, Basel, Switzerland). The 25 (OH) vitamin D level was measured by radioimmunoassay assay; 24-h urinary calcium, phosphate, and creatinine levels were also measured.

Serum osteocalcin (OC) levels, markers of bone formation, were measured with commercially available enzyme-linked immunosorbent assay (ELISA) kits (Trinity Biotech, Wicklow, Ireland). Urinary deoxypyridinoline (dPD) (adjusted for creatinine excretion) as a marker of bone resorption was measured using a chemiluminescence method with an automatic hormone analyzer (DPC Immulite, Los Angeles, Calif., USA).

Separately, hematological (hemoglobulin, folic acid, vitamin $B_{12}$, mean corpuscular volume, erythrocyte sedimentation rate, immunoglobulins, protein electrophoresis, antinuclear antibody, anti-DNA) tests were performed using routine methods. Posteroanterior chest X-rays were obtained from all patients.

### Serological tests

Both osteoporotic and control populations were screened using a similar algorithm. The protocol was based on a two-level evaluation. The first level consisted of determining serum level of IgA antigliadin antibodies.

Subjects who were negative for IgA AGA were classified as not having CD, while patients with positive IgA AGA underwent a second level of the screening process.

For the second level of screening, the serum IgA EMA test, which has a high sensitivity and specificity [19, 20], was performed. The differences between the first and second levels of screening were sensitivity and specificity. Although serum IgA AGA has been widely used in clinical practice, it has only moderate sensitivity (75–90%) and specificity (82–95%) [21]. On the other hand, the sensitivity and specificity of EMA are 97–100 and 85–98%, respectively [22, 23].

### Antigliadin antibody and antiendomysial antibody tests

The IgA AGA test (Euroimmun, Lübeck, Germany) and the IgA EMA test (Euroimmun, Lübeck, Germany) systems were used to screen for CD. Immunoglobulin A endomysial antibodies were determined by immunofluorescence using slides of monkey liver sections as antigen, and IgA AGA was also determined by immunofluorescence using slides with gluten dot from wheat as antigen. Once the biochip slides reached room temperature, 25 µl of diluted patient serum (1:5–1:10) with phosphate-buffered saline with Tween (PBS-Tween) was dropped into the antigen well on the slide. The slides with the patients' serum and the positive and negative internal controls (provided with the test system) were incubated for 30 min at room temperature. After a washing step with PBS, 20 µl fluorescein-labeled antihuman IgA antibody was placed on the slides and incubated 30 min at room temperature. After this, the slides were rinsed in PBS and washed for 5 min in PBS buffer. Glycerol/PBS were embedded in 10 µl per field and then slides were examined under fluorescent microscopy by two independent examiners. Staining of the endomysium in monkey liver and gliadin dot at a titer of 1:10 was considered positive for the IgA EMA and IgA AGA according to the test kit instructions.

### Statistical analyses

Statistical analyses were performed using the SPSS 10.0 statistical program. Student's unpaired *t*-test was used for comparison of the differences between the EMA (+) and EMA (−) patients. In EMA (+) patients, Pearson's correlation analysis was performed to assess the association between BMD and Ca, PTH, 25 (OH) vitamin D, and dPD levels.

Data were expressed as the mean ± standard deviation (SD). Differences were considered significant if the *p* values were less or equal to a level of 5% and all results are expressed with 95% confidence interval.

## Results

Of the 89 osteoporotic female patients evaluated, 17 were found to have positive IgA AGA test (19%). These IgA AGA (+) patients underwent a second-level examination for the detection of IgA EMA. According to this serological test, nine patients were found to be positive for EMA (10.11%). In the healthy control group, only one patient was positive for IgA AGA (1.3%) and EMA positivity was not detected in any of the patients.

For the statistical analysis, the data obtained from the 9 EMA (+) patients were compared with the data of the 72 patients who were negative for both IgA AGA and IgA EMA. The demographic features and bone mineral density values of these patients are shown in Table 1. When the EMA (+) patients were compared with EMA (−) patients, no significant differences were found as regards age, weight, height, BMI, and lumbar and femoral BMD values ($p > 0.05$).

Table 2 shows the laboratory findings of the EMA (+) and EMA (−) osteoporotic women. Antiendomysial antibody-positive patients showed lower values of serum Ca ($p < 0.05$) and 25 (OH) vitamin D ($p < 0.01$) and significantly higher values of PTH ($p < 0.01$) compared with the EMA (−) patients. The level of urinary dPD, a marker of bone resorption, was found to be significantly higher in EMA (−) patients ($p < 0.05$). Other laboratory measurements were comparable and there were no statistically significant differences between the groups.

**Table 1** Demographic features and BMD values of the EMA (−) and (+) patients

| | EMA (−) patients ($n = 72$) | EMA (+) patients ($n = 9$) |
|---|---|---|
| Age (years) | 35.87 ± 5.31 | 36.00 ± 5.50 |
| Weight (kg) | 63.07 ± 9.62 | 59.44 ± 7.81 |
| Height (cm) | 159.67 ± 4.70 | 158.11 ± 5.33 |
| Body mass index (kg/m$^2$) | 24.86 ± 3.30 | 23.80 ± 2.93 |
| Lumbar spine BMD (g/cm$^2$) | 0.70 ± 0.07 | 0.69 ± 0.04 |
| Femoral neck BMD (g/cm$^2$) | 0.58 ± 0.06 | 0.57 ± 0.03 |
| Lumbar spine T-score | −3.31 ± 0.71 | −3.34 ± 0.33 |
| Femoral neck T-score | −3.22 ± 0.63 | −3.10 ± 0.31 |

**Table 2** Laboratory findings of the EMA (−) and EMA (+) osteoporotic patients

| | EMA (−) patients ($n = 72$) | EMA (+) patients ($n = 9$) |
|---|---|---|
| Mean corpuscular volume (fl) | 87.66 ± 4.92 | 86.59 ± 4.10 |
| Hemoglobulin (g/dl) | 12.02 ± 1.39 | 11.72 ± 1.28 |
| Vitamin $B_{12}$ (pg/ml) | 340.78 ± 131.40 | 300.04 ± 54.23 |
| Calcium (mg/dl) | 9.28 ± 0.36 | 9.02 ± 0.28* |
| Phosphorus (mg/dl) | 3.62 ± 0.53 | 3.56 ± 0.52 |
| ALP (U/l) | 70.90 ± 16.75 | 70.44 ± 19.87 |
| 25 (OH) vitamin D (ng/ml) | 17.07 ± 5.22 | 12.11 ± 1.97** |
| Parathormone (pg/ml | 43.43 ± 15.67 | 58.48 ± 13.26** |
| Osteocalcin (ng/ml) | 7.42 ± 5.03 | 7.04 ± 3.66 |
| Deoxypyridinoline (nM/mMCr) | 7.04 ± 3.66 | 6.77 ± 1.32* |
| 24-h urinary calcium (mg/dl) | 160.77 ± 13.20 | 163.56 ± 19.42 |

*$p < 0.05$ as compared between the groups (unpaired *t*-test)
**$p < 0.01$ as compared between the groups (unpaired *t*-test)

In EMA (+) patients, there was no relationship between BMD and Ca, PTH, 25 (OH) vitamin D, and dPD levels.

## Discussion

It has been reported that gastrointestinal complications might not necessarily be included in CD [24]. Bone and muscle pains, cramps, tetany, osteoporosis, and osteomalacia are the well-known extraintestinal alterations of CD. Bone mass decrease and bone metabolism derangements are frequently present and they might be the only symptom of silent CD [4, 5, 10].

In this study, we aimed to perform serological screening for CD among premenopausal women with idiopathic osteoporosis and to investigate the bone turnover in patients who are seropositive for CD. In our patient population with idiopathic osteoporosis, we found that 9 of 89 patients (10.11%) were positive for IgA EMA. In several studies, it has been reported that the prevalence of CD in the population with osteoporosis was higher than it is estimated for the general population [16, 25]. Lindh et al. [16] have shown that the prevalence of CD in idiopathic osteoporosis was higher than it is estimated for the Swedish population. In their study, 11 of the 92 osteoporotic patients (12%) had high IgA AGA levels compared with only 3% of the control patients. A recent study by Nuti et al. [25] has also demonstrated an increase in the prevalence of undiagnosed CD in osteoporotic women with TG-ab screening. In this study, high levels of IgG AGA and TG-ab were observed in 24 of the 255 patients with a prevalence of serological disease of 9.4%. On the other hand, the results of some studies are contradictory. Gonzales et al. [26], using our screening method, found that the prevalence of CD did not show any increase in patients with low BMD and in postmenopausal osteoporotic women.

Serum calcium, 25 (OH) vitamin D, and PTH levels were found within the normal range in all patients. When the nine patients with EMA (+) test were compared with EMA (−) patients, we found a significant increase in the serum PTH and urinary dPD, and a decrease in the serum Ca and 25 (OH) vitamin D levels in EMA (+) patients. Across the entire study group, the level of 25 (OH) vitamin D, PTH, and dPD did not correlate with BMD at any site. Similar results were reported by Nuti et al. who compared the TG-ab-positive and TG-ab-negative osteoporotic patients [25]. The authors found a decrease in 25 (OH) vitamin D and an increase in PTH and urinary crosslaps. In symptomatic patients with secondary hyperparathyroidism, increased urinary markers of bone turnover have been reported [27]. It has been suggested by several authors that even in patients without gastrointestinal symptoms, CD also should be considered in the differential diagnosis of unexplained hypocalcemia or hyperparathyroidism in the presence of low or normal calcium levels [28].

The pathogenesis of osteoporosis associated with CD is not well understood. Previous studies suggested that calcium malabsorption may cause secondary hyperparathyroidism, which leads to bone resorption and a decrease in BMD [27, 29]. Additionally, intestinal inflammation and cytokines may play an important role in reducing bone mass. In some studies, it has been shown that increased cytokine production is associated with increased bone loss [30].

The prevalence of CD is greater than previously estimated and the prevalence of disease varies in different areas of the world [31]. Studies based on population screenings have estimated that the prevalence of the disease is 1 in 250 in the United States of America and 1 in 152 in Europe [32, 33]. According to the screening studies performed on osteoporotic patients, it has been estimated that the prevalence of the disease is about 9.4 and 12% [16, 25]. Since there are no published data about the prevalence of CD or about the serological screening for CD in our country, we think it is not convenient to make a comment on this subject. In this study, the prevalence of serological CD is estimated at 1.3% in our healthy controls. On the other hand, EMA positivity was found in 10.11% of our osteoporotic patients and this value appears far higher than that of the normal population.

Although our results are generally consistent with the results of previous studies, we have to admit that the results of this study are not directly comparable with the previous ones since in all of these studies, the majority of the patients were in the postmenopausal stage. We tried to eliminate other factors that would affect BMD and bone turnover and we included only premenopausal women in this study. Postmenopausal stage is one of the most important factors known to impair bone mass. In our opinion, these patients cannot be classified as having ''idiopathic osteoporosis.''

We admit that the lack of intestinal biopsy is the main limitation of our study. Although the diagnosis of CD may be suspected based on clinical or serological tests, the histology of the small intestine is still the gold standard [34]. Since only one of the nine EMA (+) positive patients consented to intestinal biopsy, none of the patients in this study underwent biopsy. On the other hand, the antiendomysial antibody screening used in our study has been accepted as the best immunological marker of CD and even in low-risk populations it has a high positive predictive value [19, 20]. When both AGA tests were combined with EMA, sensitivity of the screening protocol reaches almost 100% [22, 23]. In a study by Feighery et al. [35], intestinal biopsy and EMA were shown to have similar predictive value in the diagnosis of CD. Similarly, the results of the study by Rossi et al. [36] showed that EMA appears to be specifically correlated to the intestinal histopathology of CD and does not appear to be a nonspecific marker for mucosal atrophy. Additionally, Trier [37] has suggested that intestinal biopsies are not considered essential to make a diagnosis in adults.

In the light of the results of this study, we suggest that all patients with idiopathic osteoporosis might be screened for CD by measurement of EMA. Additionally, we believe that serological screening for CD and detection of such patients will allow determination of the most convenient treatment strategies for osteoporosis. In addition, this is the first study in which only premenopausal osteoporotic women were investigated for CD. For this reason, we believe that the results obtained in this study might suggest a new insight.

## Take home message

In the light of the results of this study, we suggest that all patients with idiopathic osteoporosis might be screened for CD by measurement of EMA.

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