# Bone Mineral Density Screening and the Frequency of Osteopenia/Osteoporosis in Turkish Adult Patients With Celiac Disease

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## ABSTRACT

**Background:** *The aim of this study was to evaluate the prevalence of osteopenia and osteoporosis in adult patients with celiac disease (CD) at diagnosis and/or in the follow-up after a gluten-free diet (GFD).*

**Methods:** *Adult patients diagnosed with CD were retrospectively screened through follow-up records and computer databases. Patients assessed by dual-energy X-ray absorptiometry (DEXA) at diagnosis and/or in the follow-up after a GFD were included in the study.*

**Results:** *One hundred patients who underwent a DEXA scan at least once after diagnosis or after being on a GFD were included in the study. The mean age of the patients at diagnosis was 34.61 ± 10.3 years, and 84% of the patients (n = 84) were female. At the time of diagnosis (n = 46), the prevalence of osteopenia and osteoporosis was 67.3% and 15.2%, respectively, at the lumbar spine, and 43.4% and 10.8%, respectively, at the femur. After a GFD (n = 78), the prevalence of osteopenia and osteoporosis was 61.5% and 8.9%, respectively, at the lumbar spine, and 37.1% and 2.5%, respectively, at the femur.*

**Conclusion:** *The prevalence of CD patients with low bone mineral density (BMD) is high after diagnosis and in the follow-up after a GFD. It is important for all patients with CD to undergo a DEXA scan to determine the follow-up and/or treatment characteristics.*

**Keywords:** *Celiac disease, bone mineral density, osteopenia, osteoporosis*

## INTRODUCTION

Celiac disease (CD), triggered by gluten, occurs in genetically predisposed individuals. It is characterized by chronic intestinal mucosal inflammation and villous atrophy, and causes damage to the absorption function of the small intestine.[1] The typical and atypical form of the disease may be accompanied by many extraintestinal manifestations.[2] Osteomalacia, osteopenia, and osteoporosis can be the presenting features or the extraintestinal manifestations of CD.

Calcium and vitamin D deficiency can lead to secondary hyperparathyroidism, which is considered to be the main reason for osteopenia and osteoporosis in patients with CD.[3] The prevalence of osteoporosis in CD was reported at highly variable ranges (6-70%), and the presence of osteoporosis was found to be associated with an increase in the risk of bone fractures.[4]

Although it is recommended to evaluate the bone mineral density (BMD) at diagnosis or in the follow-up, there is no consensus on screening time with dual-energy X-ray absorptiometry (DEXA).[5] On the other hand, some real-life data found in the literature revealed that a substantial portion of patients with CD were not screened with DEXA.[6,7]

As far as we know, there are no data on the prevalence of osteopenia and osteoporosis in adult patients with CD in our country. The different genetic and environmental factors in each cohort, as well as the diagnostic features of CD, may affect bone health. Therefore, it is crucial to know the frequency of osteopenia/osteoporosis in our CD patients. Additionally, the evaluation of the frequency of osteopenia and osteoporosis in patients without well-known osteoporosis risk factors such as advanced age and menopause may be useful in determining screening strategies.

The aim of this study was to evaluate the prevalence of osteopenia and osteoporosis in patients with CD at diagnosis and in the follow-up after a gluten-free diet (GFD).

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## MATERIALS AND METHODS

The follow-up files and the hospital's computer database records of the patients who were diagnosed with CD between January 2010 and December 2019 were evaluated retrospectively. Patients assessed by DEXA at diagnosis and/or in the follow-up after a GFD were included in the study.

A diagnosis of CD was made when an individual was positive for tissue transglutaminase immunoglobulin A (t-TGA) and/or endomysium immunoglobulin A (EMA), and demonstrated findings of at least Marsh grade II upon duodenal biopsy. Patients who were assessed by DEXA within 3 months before or after the diagnosis were considered "screened at the time of diagnosis," and those who underwent a DEXA scan at any time (at the 12th month at the earliest) after the GFD were considered "screened after a GFD." In patients screened after a GFD, the follow-up period was accepted as the time from the date of first diagnosis until the last DEXA scan date (month).

Osteoporosis was diagnosed when a patient had a T score ≤−2.5 at any localization, osteopenia was diagnosed when a patient was within the range of −1> T score >−2.5, and normal BMD was diagnosed when a patient had a T score ≥−1.[8] In addition, patients who did not have normal BMD according to the T score were defined as having low BMD. Furthermore, patients were analyzed according to the Z score (Z score <−2 or Z score ≥−2). A Z score <−2 was defined as low bone mass.[9]

Of the patients screened at the time of diagnosis, demographic characteristics (age/sex), body mass index (BMI), clinical presentation features, duodenal histopathology findings according to the Marsh classification, t-TGA and/or EMA status, menopausal status, habits of smoking or alcohol consumption, the total lumbar (L2-4) and femoral BMD values, and the T and Z scores identified by the DEXA scan were recorded.

Of the patients screened after a GFD, clinical presentation features (age/sex) and duodenal histopathology findings according to Marsh classification at the time of diagnosis were recorded. In addition, at the end of the follow-up period, the BMI, t-TGA, and/or EMA status, GFD compliance assessed by dietary history, menopausal status, smoking and drinking habits, treatments received for osteopenia or osteoporosis, the total lumbar (L2-4) and femoral BMD, and T and Z scores identified by the DEXA scan were recorded.

Patients diagnosed under the age of 17, patients with a negative t-TGA and/or EMA status at the time of diagnosis, those who had a history of steroid and levothyroxine use or endocrine disorders (hyperthyroidism, untreated hypothyroidism, hypogonadism, Cushing disease, primary hyperparathyroidism, diabetes mellitus), and patients with a malignant disease were excluded from the study.

Premenopausal women and male patients under the age of 50 years were defined as subgroups. The frequency of osteopenia and osteoporosis were analyzed.

The research was approved by the Local Ethics Committee dated April 14, 2020 and numbered B10.1.TKH.4.34.H.GP.0.01/90.

### Statistical Analysis

The patients' data were analyzed with the SPSS 25.0 program. Descriptive information about the demographic features of the patients was presented as the mean (median for those without normal distribution), frequency, and percentage. The distribution of data according to the number of samples was evaluated by the Shapiro–Wilk and Kolmogorov–Smirnov tests. The mean of continuous variables found to be normally distributed was compared with the Student's *t*-test, and the mean of non-normally distributed variables was compared with the Mann–Whitney *U*-test. Paired *t*-tests for normally distributed data and the Wilcoxon signed-rank tests for non-normally distributed data were used for comparison of repeated measurement values. Chi-squared test and Fisher's exact test were used to compare categorical data. The statistical significance level (*P* value) was accepted as <.05, and the results are given within a 95% CI.

## RESULTS

A total of 75.5% (*n* = 105) of adult CD patients (*n* = 139) were screened with DEXA at diagnosis and/or in the follow-up. After applying the exclusion criteria, 100 patients who underwent a DEXA scan at least once after diagnosis or a GFD were included in the study. The flowchart of the study is shown in Figure 1. At the time of diagnosis, the mean age of the patients was 34.61 ± 10.3 years, 84% of the patients were female, and the mean symptom duration before diagnosis was 14.2 ± 15.7 months. A total of 83% of the patients had received calcium and/or vitamin D supplements at any time after diagnosis.

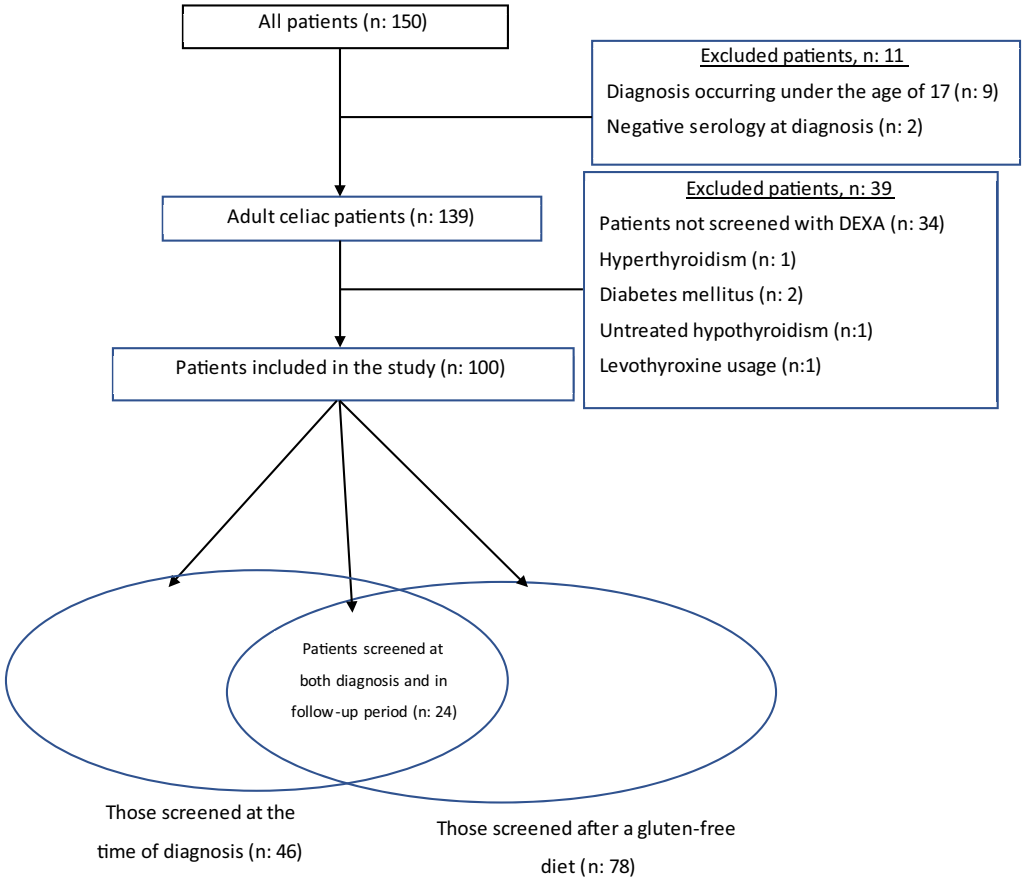


**Figure 1.** Flowchart of the study.

### *Patients Screened at the Time of Diagnosis*

The general characteristics of the patients (*n* = 46) are shown in Table 1. At diagnosis, the prevalence of osteopenia and osteoporosis was 67.3% (*n* = 31) and 15.2% (*n* = 7) at the lumbar spine, and 43.4% (*n* = 20) and 10.8% (*n* = 5) at the femur. The lumbar and femoral DEXA results of the patients screened at the time of diagnosis are shown in Table 2.

Of the female patients, 15.2% (*n* = 7) were in menopause. In addition, 2.1% (*n* = 1) were male patients over 50 years old. In the total group, the frequency of osteoporosis was 37.5% (*n* = 3).

### *Patients Screened After a GFD*

The general characteristics of the patients (*n* = 78) are shown in Table 3. The prevalence of osteopenia and osteoporosis after a GFD was 61.5% (*n* = 48) and 8.9% (*n* = 7) at the lumbar spine, and 37.1% (*n* = 29) and 2.5% (*n* = 2) at the femur. The femoral and lumbar DEXA results of these patients are shown in Table 4.

A total of 28.2% (*n* = 22) of the patients were in menopause. In these patients, the frequency of osteoporosis was 22.7% (*n* = 5).

Thirty seven percent of patients (*n* = 29) were taking supplements at the end of the follow-up period. At the end of the follow-up period, 1.2% (*n* = 1) of patients were found to have received bisphosphonate treatment.

### *Patients Screened Both at Diagnosis and After a GFD*

While on a GFD, 23.5% (*n* = 24) of the patients were reassessed by DEXA, at an average of 34.25 ± 19.5 months after diagnosis. Women comprised 87.5% (*n* = 21) of the patients (19%, *n* = 4 in menopause) and all of the male patients were under the age of 50 years. The mean age of the patients was 36.2 ± 7.1 years, at the time of diagnosis. The prevalence of osteopenia and osteoporosis in these patients was 62.5% (*n* = 15) and 16.6% (*n* = 4), respectively, at diagnosis, and 66.6% (*n* = 16) and 4.1% (*n* = 1), respectively, after a GFD. the total

**Table 1.** General Characteristics of Patients Screened at the Time of Diagnosis (*n* = 46)

| | |
|---|---|
| Age (mean ± SD) | 35.3 ± 9.8 |
| Sex, n (%) | |
| Male | 9 (19.5%) |
| Female | 37 (80.5%) |
| Male patients >50 years of age, n (%) | 1 (2.1%) |
| Woman in menopause, n (%) | 7 (15.2%) |
| BMI (kg/m$^2$) (mean ± SD) | 23.3 ± 4.1 |
| Clinical presentation, n (%) | |
| Anemia | 17 (36.9%) |
| Chronic diarrhea | 19 (41.3%) |
| Dyspepsia | 4 (8.6%) |
| Abdominal pain | 5 (10.8%) |
| Other | 1 (2.1%) |
| Positive for EMA and/or t-TGA | 46 (100%) |
| Duodenal histopathology, n (%) | |
| Marsh II | 1 (2.17%) |
| Marsh IIIA | 14 (30.43%) |
| Marsh IIIB | 19 (41.3%) |
| Marsh IIIC | 12 (26.1%) |
| Smoking, n (%) | 8 (17.3%) |
| Alcohol, n (%) | 0 |

BMI, body mass index; EMA, endomysium immunoglobulin A; SD, standard deviation; t-TGA, tissue transglutaminase immunoglobulin A.

femoral and lumbar mean BMD values and the T and Z scores were found to be significantly higher at the end of the follow-up period than at the time of diagnosis ($P < .05$) (Table 5). At the end of the follow-up period after a GFD, 50% (*n* = 12) of the patients were found to be positive for t-TGA and/or EMA, and 25% (*n* = 6) were not compliant with a GFD. All of the patients had received calcium and/or vitamin D supplements, and 4.1% (*n* = 1) of them had received bisphosphonate treatment at any time after diagnosis.

## DISCUSSION

The worldwide frequency of CD varies between 0.6% and 1%, and in Turkey, seroprevalence has been reported in the range of 0.77-1.3%.[10,11,12] CD may show various clinical presentations. Patients may have classic malabsorption symptoms that include diarrhea, steatorrhea, and weight loss. Atypical CD, which has become a more commonly diagnosed CD disease type in recent years, may present with abnormal liver function tests, arthralgia/arthritis, dermatitis herpetiformis, alopecia, anemia, stomatitis, myalgia, psychiatric disorders, epileptic seizures, neuropathy, growth retardation, delayed puberty, and infertility.[2] Apart from gastrointestinal symptoms, bone mineralization disorders are the most common manifestations of CD.[13]

In CD, decreased digestive enzymes along with a loss of the absorptive surface of the small intestine may lead to insufficient absorption of calcium, micronutrients and vitamin D taken in with the diet (14).[14] Increasing levels of pro-inflammatory cytokines (TNF-alpha, IL-1β and IL-6), other endocrinological disorders, such as secondary hyperparathyroidism and hypogonadism, and, rarely, the presence of anti-osteoprotegerin antibodies can affect bone homeostasis in CD.[15,16,17]

The presence of osteoporosis is associated with increased risk of bone fracture. Some studies have shown

**Table 2.** Bone Mineral Density Results of Patients Screened at the Time of Diagnosis (*n* = 46)

| | All Patients | | | | | |
|---|---|---|---|---|---|---|
| DEXA Localization | BMD* | T score* | Z score* | Osteopenia** | Osteoporosis** | –2 <Z score** |
| Femur | 0.843 | –1.02 | –0.79 | 20 (43.4%) | 5 (%10.8) | 6 (13%) |
| Lumbar spine | 0.883 | –1.65 | –1.27 | 31 (67.3%) | 7 (%15.2) | 11 (23.9%) |
| Premenopausal women (n = 30) | | | | | | |
| Femur | 0.825 | –1.04 | –0.88 | 14 (46.6%) | 3 (10%) | 4 (13.3%) |
| Lumbar spine | 0.880 | –1.35 | –1.25 | 20 (66.6%) | 3 (10%) | 6 (20%) |
| Male patients >50 years of age (n = 8) | | | | | | |
| Femur | 0.920 | –0.88 | –0.58 | 2 (25%) | 1 (12.5%) | 1 (12.5%) |
| Lumbar spine | 0.912 | –1.73 | –1.6 | 7 (87.5%) | 1 (12.5%) | 3 (37.5%) |

*Values are medians; **Values are *n* (%).
BMD (g/cm$^2$), bone mineral density; DEXA, dual-energy X-ray absorptiometry.

**Table 3.** General Characteristics of Patients Screened After a Gluten-Free Diet (*n* = 78)

| | |
|---|---|
| At diagnosis (n = 78) | |
| Age (mean ± SD) | 34.1 ± 7.2 |
| Sex, n (%) | |
| Male | 10 (12.8%) |
| Female | 68 (87.2%) |
| Clinical presentation at diagnosis, n (%) | |
| Anemia | 32 (41%) |
| Chronic diarrhea | 23 (29.5%) |
| Dyspepsia | 11 (14.1%) |
| Abdominal pain | 11 (14.1%) |
| Other | 1 (1.3%) |
| Duodenal histopathology at diagnosis, n (%) | |
| Marsh II | 1 (1.3%) |
| Marsh IIIA | 26 (33.3%) |
| Marsh IIIB | 37 (47.5%) |
| Marsh IIIC | 14 (17.9%) |
| After a GFD (at the time of screening) | |
| Age (mean ± SD) | 36.8 ± 7.7 |
| BMI (kg/m$^2$) (mean ± SD) | 23.79 ± 4.21 |
| Overweight | 21 (26.9%) |
| Obese | 10 (12.8%) |
| Women in menopause, n (%) | 22 (28.2%) |
| Male patients >50 years of age, n (%) | - |
| Smoking, n (%) | 12 (15.3%) |
| Alcohol, n (%) | 2 (2.5%) |
| GFD adherence, n (%) | |
| No | 17 (21.8%) |
| On a GFD | 61 (78.2%) |
| Seropositivity (positive EMA or t-TGA status) in GFD-compliant patients | 15 (24.5%) |
| Seropositivity in GFD non-compliant patients | 17 (%100) |
| Treatment, n (%) | |
| Calcium and/or vitamin D supplements | 28 (35.8%) |
| Bisphosphonate | 1 (1.2%) |
| Follow-up period (months)* | 31 (IQR:25) |

*Values are median.
BMI, body mass index; EMA, endomysium immunoglobulin A; GFD, gluten-free diet; SD, standard deviation; t-TGA, tissue transglutaminase immunoglobulin A.

that in CD, BMD increases with improvements in histopathological findings after a GFD. The British Society of Gastroenterology Guidelines for the diagnosis and management of CD recommend screening patients with osteoporosis risk factors at least 1 year after being on a GFD.[18] The European Society for the Study of Coeliac Disease (ESsCD) guidelines recommend that CD patients who have high risk factors for osteoporosis (men over 50 years of age, perimenopausal or postmenopausal women, and those with late-diagnosed, fragility fractures or diagnosed with malabsorption or bone disease) should be screened with DEXA at the time of diagnosis, and others should be screened before 30-35 years of age.[19]

We found that 24.4% of our adult CD patients had not been screened with DEXA. As in our study, some data in the literature revealed that patients with CD have been assessed by DEXA at varying rates. In one retrospective study, Fouda reported that only 36% of 128 adult patients had been assessed by DEXA, while in another study, 93% of 250 patients had been evaluated by DEXA at diagnosis and 60% in the follow-up period.[7,20] In our study, the fact that screening was not implemented for some patients may be associated with the lack of a standardized screening and/or follow-up process.

Literature data reported a low frequency of BMD, between 50% and 74%, at the time of diagnosis in untreated patients. In a study conducted by Pantaleoni et al. (*n* = 169), the prevalence of osteopenia at the lumbar vertebrae and femoral neck was 37% and 44%, respectively, and that of osteoporosis was 21% and 13%, respectively.[21,22,23] In this study, the prevalence of osteopenia at the lumbar vertebrae and femur at the time of diagnosis was 67% and 43%, respectively, and that of osteoporosis was 15% and 10%, respectively. In addition, we found that 23.9% and 13% of patients had low bone mass according to the total lumbar vertebra and femoral Z score, which indicates bone mass of patients with similar age and sex at diagnosis.

As far as we know, there are no data on the frequency of osteopenia or osteoporosis in adult CD patients in our country. We think that it is difficult to compare the literature data and the data of this study due to the differences in risk factors for osteoporosis (amount of calcium taken in compliance with diet, age, the presence of menopause, smoking, alcohol consumption, sex, exercise, and genetic factors) between the cohorts investigated and the factors associated with CD (the form of presentation, late diagnosis, the severity of villous atrophy, etc.).

The fact that most of our patients were diagnosed when the clinical signs of CD were overt, may be related to

**Table 4.** Bone Mineral Density Results of Patients Screened After a Gluten-Free Diet (*n* = 78)

| | All Patients | | | | | |
|---|---|---|---|---|---|---|
| DEXA Localization | BMD* | T score * | Z score* | Osteopenia** | Osteoporosis** | −2 < Z score** |
| Femur | 0.879 | −0.7 | −0.4 | 29 (37.1%) | 2 (2.5%) | 4 (5.1%) |
| Lumbar spine | 0.908 | −1.3 | −1.00 | 48 (61.5%) | 7 (8.9%) | 10 (12.8%) |
| Premenopausal women (n = 46) | | | | | | |
| Femur | 0.846 | −0.7 | −0.3 | 18 (39.1%) | 1 (2.1%) | 3 (6.5%) |
| Lumbar spine | 0.908 | −1.3 | −0.90 | 30 (65.2%) | - | 3 (6.5%) |
| Male patients <50 years of age (n = 10) | | | | | | |
| Femur | 0.930 | −0.7 | −0.5 | 2 (20%) | - | - |
| Lumbar spine | 0.950 | −1.3 | −1.05 | 7 (70%) | 1 (10%) | 1 (10%) |

*Values are medians; **Values are *n* (%).
BMD (g/cm$^2$), bone mineral density; DEXA, dual-energy X-ray absorptiometry.

**Table 5.** Comparison of DEXA Results of Patients Screened Both at the Time of Diagnosis and After a Gluten-Free Diet (*n* = 24)

| Parameters | At Diagnosis (mean ± SD) | After a GFD (mean ± SD) | *P* |
|---|---|---|---|
| Femoral BMD | 0.839 ± 0.098 | 0.905 ± 0.121 | **.001*** |
| T score | −0.89 ± 1.01 | −0.47 ± 1.09 | **.002*** |
| Z score | −0.77 ± 1.04 | −0.27 ± 1.11 | **.004**** |
| Lumbar spine BMD | 0.853 ± 0.212 | 0.924 ± 0.093 | **.026**** |
| T score | −1.53 ± 1.03 | −1.14 ± 0.88 | **.013*** |
| Z score | −1.31 ± 1.05 | −0.92 ± 0.93 | **.008**** |

*Paired *t*-test, **Wilcoxon signed-rank test.
BMD (g/cm$^2$), bone mineral density; GFD, gluten-free diet; SD, standard deviation.

the high rate of low bone density in this study. Recently, Tovolli et al. reported that CD patients diagnosed by screening had a significantly lower percentage of osteopenia/osteoporosis compared with those diagnosed with clinical suspicion. They concluded that early diagnosis protects from severe metabolic bone disease.[24] However, in our study, only 2 patients (screened for family history) were diagnosed without obvious clinical signs. On the other hand, moderate or severe villous atrophy was present in duodenal biopsies in two-thirds of our patients at the time of diagnosis, with findings of chronic diarrhea in more than one-third of our patients.[18,25]

Our study also revealed that 70.4% (osteopenia: 61.5% and osteoporosis: 8.9%) of the patients had low BMD after a GFD (*n* = 78). In adult CD, the main treatment for bone disease is a GFD; however, with GFD treatment, some patients achieve normal BMD levels.[26] In this study, only 21.2% of patients (*n* = 17) were not compliant with a GFD, but since 41.2% (*n* = 33) were positive for t-TGA or EMA, it can be assumed that some of the GFD-compliant patients unknowingly consumed some gluten.[19] In addition, Larussa et al.[27] found that normal BMD after a GFD in CD is associated with duodenal mucosal healing. Although we were not able to evaluate duodenal histopathology, post-GFD mucosal pathological findings are likely to persist in a significant number of our patients.

It has been reported that BMI increases in patients with GFD compliance.[28] Also, non-alcoholic fatty liver disease (NAFLD) develops in approximately one-third of the patients. It is known that chronic liver diseases increase the risk of osteoporosis. However, the relationship between osteoporosis and NAFLD is still not fully understood.[29] In this study, 26.9% (*n* = 21) of our patients were overweight and 12.8% (*n* = 10) were obese, after GFD. However, our patients were not evaluated for presence of NAFLD.

Age and menopause are common risk factors for osteoporosis. In a systematic review, Ganji et al.[30] reported the prevalence of osteopenia and osteoporosis at the time of diagnosis as 39.6% and 14.4%, in men and premenopausal women, respectively. In this study, the prevalence of osteoporosis was 10.5% at the time of diagnosis and 3.5% (*n* = 2) after a GFD in premenopausal women and men under the age of 50. In contrast, the prevalence of osteoporosis in menopausal women and in men over the age of 50 was higher (37.5% at diagnosis and 22.7% after a GFD).

The important limitations of this study are that it was a single-center and retrospective study involving a small

number of patients. The other limitations are the inability to evaluate mucosal healing and other risk factors for osteoporosis. However, we think that it is important to report the first literature data from our country that show the frequency of evaluation for bone disease in adult CD patients and the results of BMD as real-life data.

As a result, we found that the rate of patients with low BMD at diagnosis and at follow-up after a GFD was high in adult CD patients, and that BMD increased significantly after a GFD. It is important for all of these patients to undergo a DEXA scan to determine the follow-up characteristics and to receive treatment to increase the bone mass and reduce the risk of fractures. However, we think that the prevalence of osteopenia, osteoporosis, and risk factors at the time of diagnosis and in the follow-up period should be evaluated with prospective studies.

***Ethics Committee Approval:*** This study was approved by the Umranıye Training and Research Hospital Ethics Committee (April 14, 2020/B10.1.TKH.4.34.H.GP.0.01/90).

***Informed Consent:*** N/A.

***Peer review:*** Externally peer-reviewed.

***Author contributions:*** Concept – S.S.; Design – S.S., G.A.; Supervision – S.S., H.L.D.; Resources – R.K.; Materials – K.K., Ö.K., H.A., Ç.A.; Data Collection and/or Processing – K.K., Ö.K., H.A., Ç.A., R.K.; Analysis and/or Interpretation – S.S., P.G., G.A.; Literature Search – S.S., G.A.; Writing Manuscript – S.S.; Critical Review – G.A., K.Ö., N.M.B.

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