

Evaluation of the prevalence of osteoporosis in children with inflammatory bowel disease

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ABSTRACT

Objective: Inflammatory bowel disease (IBD) is a rare condition in childhood. The aim of this study is to evaluate the presence of osteoporosis in patients diagnosed with IBD.

Material and Methods: The study is retrospective design evaluating 34 patients aged 8–18 years with IBD who were followed up in the Pediatric Gastroenterology Outpatient Clinic in a tertiary hospital.

Results: Of the 34 patients who were followed up, 17 (50%) had Crohn's disease and 17 (50%) had ulcerative colitis. The osteoporosis is detected in only one (2.9%) patient, four patients (11.7%) had low lumbar vertebra (L1–L4) bone mineral density (BMD) according to age, and two patients (5.8%) had low BMD according to height and sex-adjusted for Turkish children. When adjusted for United States children, 10 (29%) patients had low L1–L4 BMD. No relationship was found between the BMD Z-score and the age at diagnosis ($r=-0.085$, $p=0.638$), and the duration of disease ($r=0.094$, $p=0.599$). A moderate positive correlation was identified between the standardized body mass index and BMD Z-score of the patients ($r=0.418$, $p=0.017$).

Conclusion: It was concluded that no relationship was found between the age at diagnosis, duration of disease, and BMD values in pediatric patients with IBD. The diagnosing of osteoporosis is difficult in children and confusing results was obtained when adjusted for population-based references. There is a need to ascertain normal standardized values for Turkish children to facilitate the standardized osteoporosis screening of patients.

Keywords: Bone mineral density; childhood; Crohn's disease; inflammatory bowel disease; osteoporosis; ulcerative colitis.

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İnflamatuvar bağırsak hastalığı olan çocuklarda osteoporoz sıklığının araştırılması

ÖZET

Amaç: İnflamatuvar bağırsak hastalığı çocuklukta nadir görülen bir durumdur. Bu çalışmada, inflamatuvar bağırsak hastalığı tanılı hastalarda osteoporoz açısından kemik mineral yoğunluğu ölçümü yapıldı.

Gereç ve Yöntemler: Bu çalışma, pediatrik gastroenteroloji polikliniğinde takip edilen, 8–18 yaş arası inflamatuvar bağırsak hastalığı tanılı 34 hastanın dosyasının retrospektif olarak incelenmesiyle yapıldı.

Bulgular: Çalışmaya alınan 34 hastadan 17'si (%50) Crohn hastalığı, 17'si ülseratif kolit (%50) tanısıyla izlenmekteydi. Türk çocukların eğrisine göre değerlendirildiğinde hastaların sadece %2,9'unda (n=1) osteoporoz saptandı. Hastaların %11,7'sinde (n=4) yaşa göre lomber vertebral (L1-L4) kemik mineral yoğunluğu düşük olarak değerlendirildi. Hastaların %5,8'inde (n=2) boya göre değerlendirilen kemik mineral yoğunluğu düşüktü. Eğer veriler Amerikan verileri ile değerlendirilirse %29 hastanın (n=10) L1-L4 vertebral kemik mineral yoğunluğu düşüktü. Kemik mineral yoğunluğu Z skoru ile beden kitle indeksi (r=0,418, p=0,017), tanı yaşı (r=0,085, p=0,638) ve hastalık süresi (r=0,094, p=0,599) arasında bir ilişki saptanmadı. Hastaların beden kitle indeksi ve kemik mineral yoğunluğu Z skorları arasında ılımlı pozitif bir korelasyon saptandı (r=0,418, p=0,017).

Tartışma: İnflamatuvar bağırsak hastalığı tanılı hastaların tanı yaşları, hastalık tipleri ile osteoporoz oranları arasında bir ilişki bulunamamıştır. Çocuklarda osteoporoz tanısını koymak zordur ve farklı toplumların verilerini kullanarak değerlendirmeler karmaşık sonuçlar verebilmektedir. Hastaların osteoporoz değerlendirmesi sırasında kendi toplumumuzun çocuklar için normal standart değerlerinin olması gerekliliği görülmüştür.

Anahtar Kelimeler: Kemik mineral yoğunluğu; çocuk; Crohn hastalığı; inflamatuvar bağırsak hastalığı; osteoporoz; ülseratif kolit.

INTRODUCTION

Inflammatory bowel disease (IBD) is a rare condition in childhood, which is a chronic bowel inflammation that has a disease course that alternates between periods of activation and remission (1). The majority of patients with IBD are classified as having ulcerative colitis (UC) or Crohn's disease (CD), while 10–15% exhibit atypical clinicopathological features that do not fit either condition and are categorized as having "indeterminate colitis" (2). One patient out of four is diagnosed in childhood (3). Patients may present with such classical symptoms as severe abdominal pain, rectal bleeding, and diarrhea, while others may have a silent disease course manifesting with an initial symptom of growth retardation. The presence of inflammation in IBD, a disease course characterized by activations, repeated steroid induction therapies, frequent infections, decreased physical activity, growth retardation, and malnutrition lead to osteoporosis. Due to these factors, bone remodeling and height are inhibited and experience a growth spurt. There have been many studies to date conducted with adult patients about osteoporosis. In their study, Dilekçi et al. (4) reported osteoporosis in 22.5% and 25% of patients with UC and CD, respectively. A study of children revealed a rate of osteopenia/osteoporosis of 15% following a diagnosis of IBD (5), which is notably high. Osteopathy is diagnosed in later periods in children with IBD, and particularly in those with CD (6). The inability to reach sufficient bone mineral density (BMD) in puberty and early adulthood results in osteoporosis-related fractures in advancing age. The diagnosis is based on dual-energy X-ray absorptiometry (DXA) results. In adult patients, osteoporosis is defined as a DXA T-score of -2.5 or below in postmenopausal females or age-matched males by the World Health Organization (7, 8). Diagnosing osteoporosis is somewhat

challenging in pediatric patients. According to the criteria determined by the International Society for Clinical Densitometry (ISCD), low BMD is defined as BMD two standard deviations below the average on DXA. That said, a diagnosis of osteoporosis should not be based solely on densitometric measurements, as a diagnosis requires a low BMD Z-score for age and sex, and a history of a significant fracture caused by a low-energy trauma (two upper extremities, one lower extremity, or vertebral fracture) (9). The aim of this study is to investigate the prevalence of osteoporosis and low BMD in pediatric IBD patients through using DXA to increase the awareness of osteoporosis.

MATERIAL AND METHODS

The records of a total of 34 patients who were followed up and treated in the Pediatric Gastroenterology Clinic Adana City Training and Research Hospital between September 18, 2017, and June 30, 2022, were reviewed retrospectively. Patients, diagnosed with IBD, were based on laboratory investigations and the histopathological examination of colonoscopic biopsy was included. The study was launched after approval by the Adana City Training and Research Hospital Ethics Committee (Meeting Number: 109, Date: July 04, 2022, Decision Number: 2027). The study is complied with Declaration of Helsinki. Pubertal patients aged 8–18 years with no comorbid conditions were included in the study. Patients with comorbid diseases or complications that may cause osteoporosis (osteogenesis imperfecta, metabolic disease, immobility, cerebral palsy, and operation of bowel) were excluded from the study. The data were obtained from the patient charts, including age at diagnosis, type of IBD, medications used, response to therapy, and DXA results. DXA reports after 1 year from the diagnosis were includ-

ed, scanning up to 1 year after diagnosed were excluded from the study. All patients underwent BMD measurement using a GE Healthcare Lunar DXA system device.

The data were analyzed using IBM SPSS Statistics (Version 21.0). A Shapiro-Wilk test was used to determine whether the study parameters were normally distributed. After checking the distribution of normality, the parameters with a normal distribution were compared between groups with a Mann-Whitney U-test, and Spearman's rank correlation coefficient was used to determine the relationship between continuous variables that were not normally distributed.

RESULTS

Of 34 patients 15 (44%) were female, and 19 (56%) were male; 17 (50%) had CD and 17 (50%) had UC. The median age at diagnosis was 13.4 (2.3–17.9) years, and the median duration of follow-up was 2 (1.1–10.8) years. The Z-score of the anthropometric measurements was calculated using <https://www.ceddcozum.com> software for Turkish children (10). The mean SDS for weight was -1.6 ± 1.2 , the mean SDS for height was -0.8 ± 1.16 , and the mean SDS for BMI was -1.57 ± 1.4 . No relationship was found between the age at diagnosis ($r=-0.085$, $p=0.638$), the duration of disease ($r=0.094$, $p=0.599$), and L1–L4 age-adjusted Z-score. An analysis of response to therapy revealed that 17 patients were in remission after steroid induction therapy and were maintained on classic therapy, while 17 patients were switched to biological agents at the time of BMD. In the analysis of response to therapy, no difference was found in the BMD Z-scores of the steroid responders and non-responders ($p=0.705$). The demographic features are shown in Table 1. BMD results were evaluated according to the age- and sex-adjusted references for Turkish children using <https://www.ceddcozum.com/BoneMineralDensity> software (11). When the study subjects were categorized into UC and CD patients, no significant difference was found in the L1–L4 BMD Z-scores by sex and age ($p=0.558$), by sex and height ($p=0.389$), and by sex and age compared to US children ($p=0.429$). UC patients had lower results for femur neck (FN) (g/cm^2) ($p=0.007$) FN height adjusted Z score ($p=0.031$) and FN Z-scores compared to American children ($p=0.014$) (Table 2). There was a moderate positive correlation between the BMI SDS and BMD Z-score of the patients ($r=0.418$, $p=0.017$) (Fig. 1).

DISCUSSION

In our study, we demonstrate the low BMD results of IBD patients. When the BMD (g/cm^2) results were evaluated according to age, sex, and height in Turkish children, conflicting results were obtained. Four patients (11.7%) had low BMD according to age, and two patients (5.8%) had low BMD according to height and sex. FN Z scores were lower in CD than UC patients. Osteoporosis is diagnosed in only one patient (2.9%).

IBD is a disease, in which the gastrointestinal tract is severely affected due to chronic inflammation, recurrent infection, and malabsorption, all of which result in osteoporosis. In studies of IBD, the prevalence of osteoporosis was 2–9% among patients

Table 1. Bone mineral density measurements and Z-score of the patients

	Mean±SD
Femoral neck (mg/cm^2)	863±226
L1–L4 (g/cm^2)	896±234
L1–L4 age-adjusted Z-score	0.35±2.2
L1–L4 height-adjusted Z-score	1.35±1.9
L1–L4 USA	-1.3±1.24
FN height-adjusted	1.24±2
FN USA	-0.94±1.48

SD: Standard deviation; L1–L4: Lumbar vertebra; FN: Femoral neck; USA: Normative values recorded in the United States using the GE Healthcare Lunar DXA system device.

Table 2. Bone mineral density measurements and Z-score of UC and CD patients

	UC (n=17)	CD (n=17)	p
Femoral neck (g/cm^2)	0.981±0.261	0.774±0.171	0.007*
L1–L4 (g/cm^2)	0.967±0.256	0.818±0.218	0.088
L1–L4 age-adjusted Z-score	0.74±2.14	-1.52±1.27	0.558
L1–L4 height-adjusted Z-score	1.43±1.68	1.2±2.1	0.389
L1–L4 USA	-1.12±1.3	-1.52±1.27	0.429
FN height-adjusted	2.2±1.91	0.14±2.28	0.031*
FN USA	-0.2±1.73	-1.30±1.19	0.014*

*: UC: Ulcerative colitis; CD: Crohn's disease; SD: Standard deviation; L1–L4: Lumbar vertebra; FN: Femoral neck; USA: Normative values recorded in the United States using the GE Healthcare Lunar DXA system device, $p<0.05$: Statistically significance.

with UC (12, 13) and 7–15% among patients with CD (13, 14). The risk of fracture in these patients is 40% greater than in the healthy population (15). The age at initial diagnosis and being diagnosed before the age of 18 are factors that result in a further decrease in bone mass (16). Osteoporosis affects not only patients with IBD but also patients with diseases characterized by inflammation (17). Osteoclast activation in association with increased release of proinflammatory cytokines. Increased bone destruction occurs as a result of the release of receptor activator of nuclear factor kappa-B ligand (RANKL) (18). These anorexigenic cytokines affect muscle breakdown and trigger osteoporosis (19). Low body weight and low BMI have been identified as risk factors associated with low BMD and osteoporosis in patients with CD (20). The mean SDS for weight in the present study was -1.6 ± 1.2 and the mean SDS for height was -0.8 ± 1.16 , showing values below average. The mean SDS for BMI was -1.57 ± 1.4 . Of the patients, ten had mild malnutrition, three had moderate malnutrition and three had severe malnutrition, revealing that 47% of the patients (16 patients) were malnourished. Al-

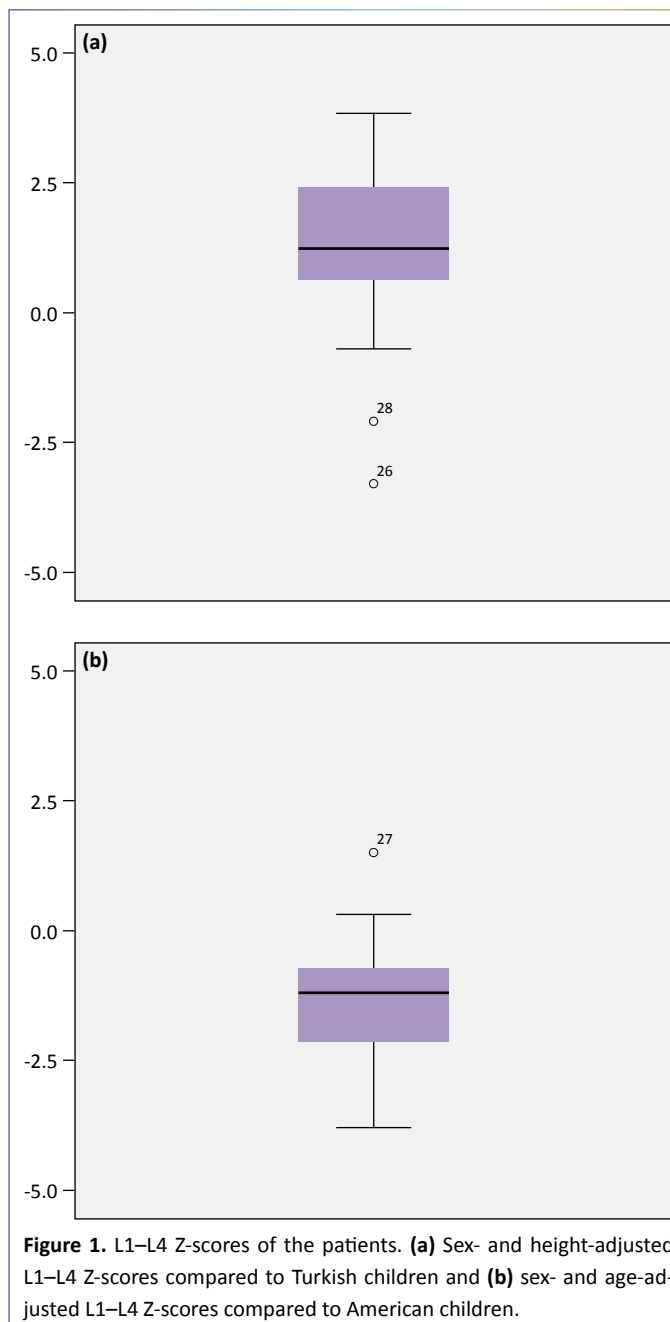


Figure 1. L1–L4 Z-scores of the patients. **(a)** Sex- and height-adjusted L1–L4 Z-scores compared to Turkish children and **(b)** sex- and age-adjusted L1–L4 Z-scores compared to American children.

though a positive relationship was found between the BMI SDS and L1–L4 age and sex adjusted Z-score, it was not found to be statistically significant due to low number of patients with low BMD. In a Korean study of adolescents, the BMD Z-scores were found to be below -2.0 in 25 of 119 patients (21%) with IBD. In a study evaluating BMD in 32 Turkish children with IBD, 14 of the patients (43.7%) were found to have either osteopenia or osteoporosis (21). Unfortunately “osteopenia” is not a terminology used for children, for this reason, we recommend the authors to re-evaluate their Z scores. In our study, according to the reference values for the United States, ten patients (29%) had low BMD Z scores (22). The point of interest in this regard are the values adjusted for Turkish children seems to underdiag-

nosed osteoporosis. The ISCD has concluded in 2019 that; “low bone mineral mass or BMD” is the preferred term for pediatric DXA reports when bone mineral content (BMC) or areal BMD Z-scores are ≤ -2.0 SD. In children with growth delay or short stature, spine and total body less head (TBLH) areal BMD and BMC results should be adjusted. For the spine, adjust using either height Z-score or the bone mineral apparent density. For TBLH, adjust using the height Z-score. After this evaluation of DXA, an appropriate reference data set for children must include a sample of healthy representatives of the general population sufficiently large to capture variability in bone measures that take into consideration gender, age, and race/ethnicity (9, 23).

In a study of children with IBD, the mean DXA BMD Z-score was -0.75 ± 0.98 , which was lower than the population average, whereas, in our study, the mean height-adjusted Z-score was 1.35 ± 1.9 . The US reference data are lower, with a mean Z-score of -1.3 ± 1.24 and it seems more reliable. In the only study establishing Turkish reference values, Gökşen et al. (11) collected the data of 345 healthy children using a Hologic QDR 4500A Fan Beam X-ray Bone Densitometer (Hologic, Bedford, MA), as we used in our study for Turkish references. Using their references, high BMD values were obtained, this result is unexpected. As such, there is an urgent need to establish reference BMD values for healthy Turkish children. The authors suggest that it would be appropriate to use the reference values for US children for comparison, until new Turkish references were collected.

Many studies have reported low 25-hydroxy (OH)-vitamin D levels in children with IBD (24, 25). Vitamin D is a regulator of calcium homeostasis and is also essential for bone health. Although low vitamin D levels have been demonstrated in this particular patient group, no association has been identified between low BMD and low 25-OH-vitamin D levels (24, 26). Although gastroenterologists commonly recommend the use of vitamin D supplements, the efficacy of vitamin D against the loss of BMD has not been clinically proven in patients with active IBD (8, 27). Nonetheless, the American Gastroenterological Association and the Endocrinology Associations all recommended regular use of 25-OH-vitamin D supplements (28). For this reason, patients would benefit from close follow-up for vitamin D supplementation and other precautions related to the protection of bone health (29). Unfortunately, most of patients’ 25-OH-vitamin D levels were not screened. We believe; therefore, that patients must be supported in the performance of regular exercise and regular vitamin D supplementation, and in the sufficient intake of calcium, most of which were also ignored during our patients’ follow-up.

CONCLUSION

It was concluded that no relationship was found between the age of diagnosis, duration of IBD, and BMD values in pediatric patients with IBD. For evaluating BMD, DXA Z scores must be interpreted according to sex-, age-, and height-adjusted population references. In Turkish pediatric population, reference values do not fit the new DXA devices and new reference val-

ues are urgently needed. As expected, the mean BMD Z score was -1.3 ± 1.24 in IBD pediatric patients, which was much lower than healthy children. Because most of them are short, malnourished and steroid using, we further recommend that clinicians must approach Z-scores in Turkish children with suspicion if measurements have been made using new devices, and particularly if there is a history of fracture. When necessary, the Z-scores of children of other nationalities established using the same device must be used.

Ethics Committee Approval: The Adana City Training and Research Hospital Clinical Research Ethics Committee granted approval for this study (date: 04.07.2022, number: 109).

Informed Consent: Written informed consent was obtained from the families of the patients who participated in this study.

Conflict of Interest: No conflict of interest was declared by the authors.

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Authorship Contributions: Concept – DGT, AA; Design – AA; Supervision – AA; Fundings – DGT, AA; Materials – DGT; Data collection and/or processing – DGT; Analysis and/or interpretation – DGT, AA; Literature review – DGT, AA; Writing – DGT; Critical review – AA.

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Hasta Onamı: Yazılı hasta onamı bu çalışmaya katılan hastaların ailelerinden alınmıştır.

Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Mali Destek: Yazarlar bu çalışma için mali destek almadıklarını beyan etmişlerdir.

Yazarlık Katkıları: Fikir – DGT, AA; Tasarım – AA; Denetleme – AA; Kaynaklar – DGT, AA; Malzemeler – DGT; Veri Toplanması ve/veya İşlemesi – DGT; Analiz ve/veya Yorum – DGT, AA; Literatür Taraması – DGT, AA; Yazıyı Yazan – DGT; Eleştirel İnceleme – AA.

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