Rev Osteoporos Metab Miner. 2022;14(4):125-130

Usefulness of the trabecular bone score in adult subjects with osteogenesis imperfecta

DOI: http://dx.doi.org/10.4321/S1889-836X2022000400005en

Florez H[1], Muxi A[2], González E[3], Monegal A[1], Guañabens N[1], Peris P[1]
1 Bone Metabolic Pathology Unit. Rheumatology Service. Hospital Clinic. IDIBAPS, CIBERehd, University of Barcelona (Spain)
2 Nuclear Medicine Service. Hospital Clinic. Barcelona (Spain)
3 Immunology Laboratory. Hospital Clinic. Barcelona (Spain)

Date of receipt: 21/02/2022 - Date of acceptance: 10/10/2022

This work was funded by a FEIOMM ASBMR 2018 grant.

Summary

Objective: To analyze the usefulness of the trabecular bone score (TBS) in adults with osteogenesis imperfecta (OI) and its relationship with clinical, anthropometric and densitometric variables, especially with the presence of fractures and the severity of the disease.

Material and methods: Cross-sectional study conducted in 31 adult patients with OI (age 40.5±15.2 years, 68% women, 87% type I). The clinical characteristics of the patients (fractures, type of OI, BMI and treatment), bone mineral density (BMD) (using DXA), assessing the presence of densitometric osteoporosis, and TBS values (TBS iNsight), estimating the presence of degraded microarchitecture (values <1.230). The results were compared between the different OI types (I and III-IV) and with those of a control group of healthy subjects.

Results: Most of the patients (29/31, 94%) had a history of fractures and 29% received antiosteoporotic treatment. 61% had densitometric osteoporosis and 19% had degraded microarchitecture. No differences were observed in the TBS values according to OI severity (OI type I vs. III-IV: 1,297 vs. 1,339, p=n.s.); no patient with OI type III-IV had TBS <1230. TBS values were related to age (r=-0.6, p<0.01), lumbar BMD (r=0.4, p=0.03) and BMI (r=-0.5 , p=0.01). Patients with OI had lower values of TBS and BMD than the control group in all locations analyzed.

Conclusion: TBS is not very sensitive in assessing bone quality in OI, since none of the patients with severe OI had a degraded microarchitecture and this was only observed in 19% of patients with OI despite presenting a high prevalence of fractures.

Key words: osteogenesis imperfecta, trabecular bone score, TBS.

Introduction

Osteogenesis imperfecta (OI) is a congenital disease that comprises a heterogeneous group of clinical and genetic disorders of connective tissue, mainly caused by mutations in the *COL1A1* and *COL1A2* genes of type I collagen. It has been estimated that the incidence of OI is approximately 1:10-20.000[1-4] and the clinical manifestations can vary from almost asymptomatic forms to very severe cases. The main characteristic of this entity is bone fragility, due to a decrease in bone mass, cortical thickness and an alteration in the trabecular architecture which, together with defects in the bone matrix, affect its quality and resistance, and lead to to a marked increase in the risk of fracture, evident from childhood[1-3,5]. Classically, OI was considered an autosomal dominant genetic disorder and patients were classified into four subtypes based on clinical severity (classification by Sillence et al.[6]: type I being the mildest, followed by types IV, III and type II, the most severe that confers perinatal mortality). Over the years new genes and pathogenic variants have been identified, adding new groups to the classification (OI type V - type XX)[1,2,4,5]. However, this classification is no longer practical and some authors prefer to classify patients according to the degree of clinical involvement of the OI (mild, moderate, severe, lethal), including the genetic defect they present[4].

Although the diagnosis of certainty is obtained with the genetic study, in routine clinical practice, this can be done based on clinical and radiological findings and family history[1,3,7]. Dual-energy X-ray absorptiometry (DXA), the gold standard technique for the diagnosis

Correspondence: Helena Flórez (hflorez@clinic.cat)

and monitoring of osteoporosis (OP), is also of some use in patients with OI. However, by providing information on bone mineral density (BMD), which is not necessarily affected in this entity, and not on bone quality, a key aspect in OI, its results must be evaluated with caution, since has shown a clear relationship between BMD values by DXA and the severity of OI[7,8]. Therefore, new diagnostic methods applicable in routine clinical practice are necessary to assess other aspects of bone quality in this process. It has been suggested that the trabecular bone score (TBS), a parameter obtained from the measurement of a gray scale of the bone texture of the 2D DXA image of the lumbar spine, could be useful in this assessment[9]. In fact, TBS values have a good correlation with bone microstructure parameters obtained by high-resolution peripheral computed tomography (HRpQCT)[10] and have been related to the development of fractures in the population independently of BMD values[9], for what has been indicated that TBS could be a good method to assess other determining parameters of bone quality, especially those related to its microstructure.

The objective of this study is to analyze the usefulness of TBS in adult subjects with OI and its relationship with clinical, anthropometric and densitometric variables, especially with the presence of fractures, as well as to compare TBS values with those of a control group of healthy individuals.

Material and methods

A cross-sectional study has been carried out in adult patients with OI who follow control and treatment in a specialized consultation of bone metabolic disease of our hospital's rheumatology service. The study protocol followed the standards of the Declaration of Helsinki and was approved by the hospital's ethics committee. The included patients signed the informed consent.

A total of 31 adult patients diagnosed with OI (21 women/10 men) have been included (after genetic study and/or compatible family history). The clinical characteristics (including weight, height and calculation of the body mass index [BMI]), presence of fractures, type of OI and previous treatments carried out were analyzed. In all patients, BMD in the lumbar spine and proximal femur was analyzed by DXA (Lunar Prodigy equipment, General Electric Medical Systems, WI, USA) to assess the presence of densitometric OP (defined by T-score values ≤−2.5 SD [in subjects ≥50 years] or Z-score <−2 SD [in subjects <50 years]), osteopenia (T-score >-2.4 and ≤−1 SD) or normal BMD (T-score > -1 SD)[11]. TBS was calculated using TBS iNsight software (version 3.0.2.0) (Medimaps group, Geneva, Switzerland) on lumbar spine DXA images; a TBS value <1.230 was considered microarchitecture degraded, between 1.230-1.310 microarchitecture partially degraded and TBS >1.310 normal[12]. The results of the TBS were compared with those of a control group of healthy subjects of similar age, gender, and BMI (n=28, 71.4% women, 39 years old on average [21-60]), from the same geographical area and who collaborated in the TBS-SEIOMM study to obtain normal TBS values in our population.

Statistic analysis

Statistical analyzes were performed using the SPSS program (version 27) (IBM Corp., NY, USA). Quantitative variables are described by mean and standard deviation (S.D.) of the mean and qualitative variables by frequency and percentages. The differences between means of the continuous variables have been analyzed using the t-test and the non-parametric Wilconxon-Mann-Whitney test, and the differences between proportions using the chi-square test or the Fisher test. To assess association between variables, the Pearson correlation coefficient was used. Results with a value of $p<0.05$ have been considered significant.

Results

A total of 31 patients (67,7% women) with a mean age of 40,5±15,2 years (range 19-70) diagnosed with OI were included. Most patients had type I OI (n=27, 87.1%), two patients had type IV OI (6.5%) and two patients had type III OI (6.5%). 29/31 (93,5%) patients had a history of fragility fractures, being multiple fractures in most cases, and only two patients with OI type I had not presented fractures. At the time of assessment, 21/31 subjects were receiving (n=9) or had received (n=12) anti-osteoporotic treatment for a mean of 65±50 months, most with bisphosphonates (oral n=15, intravenous n=11), 3 patients with teriparatide, 2 with selective estrogen receptor modulators and 1 with denosumab. The main characteristics of the patients are summarized in table 1.

When TBS values were analyzed, the mean was 1.302±0.175 [0.737-1.510]; 6/31 patients (19%) had a degraded microarchitecture, 26% a partially degraded microarchitecture, and more than half (55%) had normal TBS values; of the 6 patients with degraded microarchitecture (<1230), all of them were >40 years old, 50% were women and half also had osteoporosis, all had type I OI and 5/6 patients had a history of fractures, multiple in all cases. The sensitivity of TBS in the evaluation of patients with OI and fractures was only 17%.

Regarding BMD, 61% of patients had densitometric OP, 36% had osteopenia, and only one patient had normal BMD. There were no significant differences in terms of TBS or BMD values depending on whether the patients were receiving active anti-osteoporotic treatment at the time of assessment.

When TBS values were analyzed according to the severity of the disease (OI type I vs. type III-IV), no significant differences were found between both groups of patients (table 1 and figure 1A), nor in relation to BMD values in the proximal femur (neck and total), age or BMI; however, patients with OI type III-IV presented lower BMD values at the lumbar level and a greater number of fractures (table 1). On the other hand, when these same parameters were compared according to the number of fractures (OI patients with ≤10 vs. >10 fractures), there were no significant differences between both subgroups. It is noteworthy that no patient with OI type III or IV presented degraded microarchitecture, however, all of them presented osteoporosis in the BMD (table 1). However, the TBS values were significantly lower than those of the control group, as were the BMD values in all locations analyzed (table 2 and figure 1B).

TBS values were positively related to lumbar BMD ($r=0.4$, $p=0.03$), and negatively related to age ($r=-0.6$, $p<0.01$) and BMI ($r=-0.5$, $p=0.01$) (figure 2).

Table 1. Clinical characteristics of patients with osteogenesis imperfecta

	All n=31	OI type I n=27	OI type III-IV n=4	p
Age (years) (mean ± S.D., [range])	40.5±15.2 [19-70]	41.2±15.7 [19-70]	35.8±11.2 [25-49]	0.550
Sex (W [n, %] / M [n, %])	21 (68%)/10 (32%)	19 (70%)/8 (30%)	2 (50%)/2 (50%)	0.416
OI type I/III/IV (n, %)	27 (87.1%)/ 1 (3.2%)/3 (9.7%)	-	-	-
Patients with fractures (n, %)	29 (93.5%)	25 (92.6%)	4 (100%)	0.574
Number of fractures (mean ± S.D., [range])	11.1±12.2 [0-50]	8.6±9.4 [0-37]	28.3±16.7 [10-50]	0.012*
Current anti-osteoporotic treatment (n, %)	9 (29%)	8 (29.6%)	1 (25%)	0.849
Previous anti-osteoporotic treatment (n, %)	12 (38.7%)	9 (33.3%)	3 (75%)	0.096
Weight (kg) (mean ± SD)	59.5±11.5	60.97±10.7	49.28±13.25	0.094
Height (m) (mean ± S.D.)	1.53±0.14	1.56±0.1	1.32±0.14	0.005*
BMI (kg/m^2)(mean ± SD)	25.5±4.1	25.1±4.2	28.0±2.4	0.107
DMO lumbar (g/cm^2)	0.868±0.153	0.890±0.150	0.716±0.062	0.019*
DMO cuello femoral (g/cm^2)	0.762±0.135	0.770±0.141	0.693±0.016	0.467
DMO fémur total (g/cm^2)	0.826±0.163	0.819±0.163	0.887±0.190	0.744
T-score in the lumbar spine (mean ± S.D.)	-2.73±1.36	-2.52±1.35	-4.05±0.37	0.030*
T-score in the femoral neck (mean ± S.D.)	-2.11±1.08	-2.04±1.12	-2.7±0.36	0.278
T-score in total femur (mean ± S.D.)	-1.68±1.43	-1.73±1.41	-1.30±1.92	0.856
Z-score in the lumbar spine (mean ± S.D.)	-2.22±1.31	-2.04±1.30	-3.45±0.31	0.052
Z-score in the femoral neck (mean ± S.D.)	-1.56±0.97	-1.50±1.02	-2.00±0.30	0.215
Z-score in total femur (mean ± S.D.)	-1.25±1.32	-1.33±1.30	-0.67±1.62	0.743
TBS (mean ± S.D.)	1.302±0.175	1.297±0.183	1.339±0.117	0.932
Densitometric osteoporosis (n, %)	19/31 (61.3%)	15/27 (55.6%)	4/4 (100%)	0.089
Patients with degraded TBS (n, %)	6/31 (19.4%)	6/27 (22.2%)	0/4 (0%)	0.377

S.D.: standard deviation; W: women; M: men; OI: osteogenesis imperfecta; BMI: body mass index. *: statistically significant result. Degraded microarchitecture was considered TBS values <1.230.

Discussion

Our study results suggest that TBS may not be a useful tool to assess bone strength in patients with OI. Thus, most patients with OI had TBS values in the normal range and only 19% of them, despite having a high incidence of fractures, had degraded microarchitecture values. Likewise, no differences were observed in the TBS values in relation to the severity of the disease (OI type I vs. type III-IV) and no patient with severe disease had degraded microarchitecture, suggesting a low sensitivity of this parameter in the estimation of bone quality in this disease. To date, there are hardly any studies that analyze the usefulness of TBS in OI. Kocijan et al.[7] examined the values of TBS in a cohort of 30 adult patients (>18 years) with OI, and as in our study, they found no differences in relation to the severity of the disease (comparing individuals with OI type III-IV vs. type I). Although, they also observed differences when they compared the values with those of a control group of healthy subjects. In said study, it was indicated that TBS could be a useful tool, especially to estimate a severe deterioration of bone microstructure in OI when the values are low. However, despite having presented multiple fractures, only 19% of our patients with OI had low TBS values (degraded microarchitecture), and in our study this parameter did not differentiate patients with greater disease severity, which suggests that it is an insensitive tool to assess bone quality in OI.

It should be mentioned that the TBS values were especially related to the age of the individual. In fact, all patients with OI and low TBS values (degraded microarchitecture) were over 40 years old, with a mean age of 57 years, the age at which there is usually a progressive decrease in TBS values in the general population. Therefore, it should be remembered that there are other factors that must be taken into account when assessing TBS, such as age and BMI[3]. In this sense, both in healthy subjects and in individuals with OP, lumbar TBS, like BMD, decreases with age[14], at the same time as, and contrary to BMD, there is a negative correlation with BMI[15]; findings, as indicated, also observed in our cohort of patients with OI (figure 2).

Figure 1. (1A) TBS values in patients with osteogenesis imperfecta type I (mild) and type III-IV (severe-moderate). (1B) TBS values in patients with osteogenesis imperfecta and in the control group

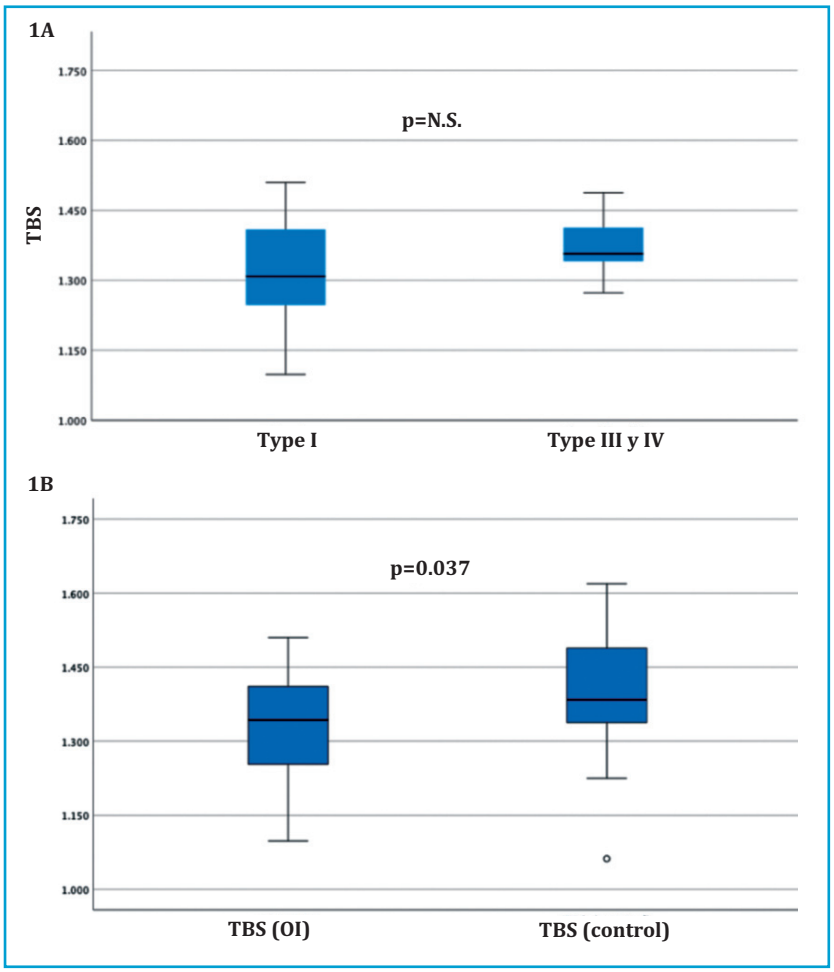


Table 2. TBS and BMD values in patients with osteogenesis imperfecta and in the control group

	Patients with OI	Control group	p
TBS	1.297 ± 0.180	1.399 ± 0.119	0.037
Lumbar BMD (g/cm^2)	0.887 ± 0.149	1.122 ± 0.172	<0.01
Femoral neck BMD (g/cm^2)	0.775 ± 0.135	0.969 ± 0.129	<0.01
Total femur BMD (g/cm^2)	0.844 ± 0.161	0.986 ± 0.124	<0.01
Lumbar T-score	-2.55 ± 1.32	-0.49 ± 1.39	<0.01
Femoral neck T-score	-1.98 ± 1.06	-0.19 ± 0.90	<0.01
Total femur T-score	-1.50 ± 1.41	-0.24 ± 0.86	<0.01
Lumbar Z-score	-2.09 ± 1.29	-0.07 ± 1.17	<0.01
Femoral neck Z-score	-1.46 ± 0.93	-0.20 ± 0.83	<0.01
Total femur Z-score	-1.11 ± 1.28	-0.02 ± 0.81	<0.01

TBS: trabecular bone score; BMD: bone mineral density; OI: osteogenesis imperfecta.
All variables are expressed as mean ± S.D. (standard deviation).

Another aspect to highlight is that 61% of our patients had a densitometric OP, and only one patient had a normal BMD, with BMD values being lower than those of the control group in all locations analyzed (lumbar spine and proximal femur). Again, these results coincide with those reported in some previous studies[16], and indicate that, although with limitations and pending the availability of better instruments in the future, the quantification of BMD continues to be, to date, the tool available in the most effective routine clinical practice to estimate the risk of fracture in these patients[1,3,5,7,16,17], despite not being able to assess the alterations in bone quality that patients with OI present.

Other techniques, such as HrpQCT, could be especially useful in assessing bone strength and quality in this entity by allowing BMD to be quantified three-dimensionally and evaluating the structure of trabecular and cortical bone in peripheral regions. Thus, in patients with OI, it has been indicated that HRpQCT, by analyzing microstructural parameters, would allow a better assessment of the severity of bone involvement, especially when compared to other techniques, such as BMD and TBS[7]. In this sense, patients with more severe forms of the disease (OI types III and IV) usually present worse structural parameters, with a greater decrease in the thickness and number of trabeculae and greater space between them[7,18]. Although, as previously indicated, it has been suggested that TBS could also provide information on bone microstructure parameters[9,10], in patients with OI the correlation between structural parameters assessed by HRpQCT and TBS is very low[7], indicating the need to assess the usefulness of this tool in these patients.

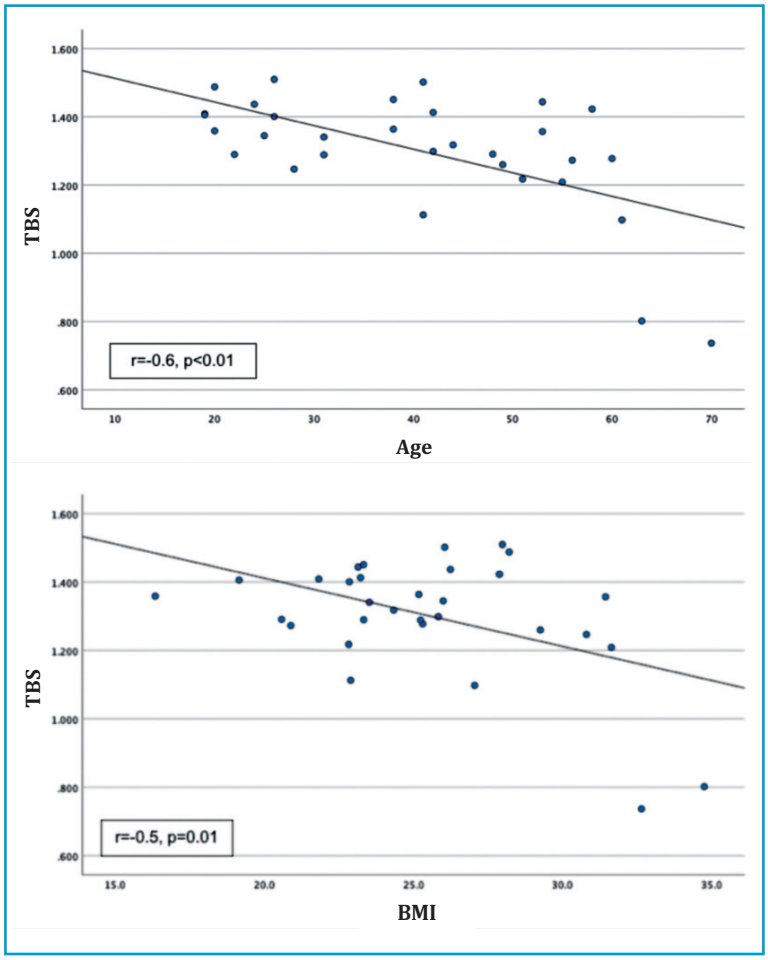
This study has several limitations, such as: the small number of patients with severe OI (types III and IV), an intrinsic limitation to the characteristics of the disease, since it deals with the less frequent types of OI. Or, the possible effect on TBS values that the antiosteoporotic treatment

followed by some of the patients included in the study may have had, a limitation also associated with this type of disease in which treatment, especially with bisphosphonates, is frequent. when there are multiple fractures, a fact present in most of our patients.

In conclusion, our study shows a low sensitivity of TBS in the assessment of bone fragility in OI, since a low percentage of patients with OI presented low values (degraded microarchitecture) of TBS, despite having suffered multiple fractures and no patient with severe OI (types III and IV) presented a degraded microarchitecture. In this study, TBS did not provide advantages in determining BMD. However, additional studies are recommended to confirm these results and include a larger number of patients with this disease, in which new tools are needed to assess bone quality and strength.

Conflict of interests: The authors declare no conflict of interest.

Figure 2. Correlation between TBS values and age and BMI



Bibliography

1. Marini JC, Dang Do AN. Osteogenesis Imperfecta. 2020. In: Feingold KR, Anawalt B, Boyce A, et al., editors. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000–. Disponible en: https://www-ncbi-nlm-nih-gov.sire.ub.edu/books/NBK279109/.
2. Marom R, Rabenhorst BM, Morello R. Osteogenesis imperfecta: an update on clinical features and therapies. Eur J Endocrinol. 2020;183:R95-R106.
3. Subramanian S, Viswanathan VK. Osteogenesis Imperfecta. 2021. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan. Disponible en: https://www-ncbi-nlm-nih-gov.sire.ub.edu/books/NBK536957/-
4. Bou Torrent R. Osteogénesis imperfecta. Protoc diagn ter pediatr. 2020; 2:349-359.
5. Ralston SH, Gaston MS. Management of Osteogenesis Imperfecta. Front Endocrinol (Lausanne). 2020;10:924.
6. Sillence DO, Senn A, Danks DM. Genetic heterogeneity in osteogenesis imperfecta. J Med Genet. 1979;16:101-16.
7. Kocijan R, Muschitz C, Haschka J, Hans D, Nia A, Geroldinger A, et al. Bone structure assessed by HR-pQCT, TBS and DXL in adult patients with different types of osteogenesis imperfecta. Osteoporos Int. 2015;26:2431-40.
8. Rehberg M, Winzenrieth R, Hoyer-Kuhn H, Duran I, Schoenau E, Semler O. TBS as a Tool to Differentiate the Impact of Antiresorptives on Cortical and Trabecular Bone in Children With Osteogenesis Imperfecta. J Clin Densitom. 2019;22:229-235.
9. Silva BC, Walker MD, Abraham A, Boutroy S, Zhang C, McMahon DJ, et al. Trabecular bone score is associated with volumetric bone density and microarchitecture as assessed by central QCT and HRpQCT in Chinese American and white women. J Clin Densitom. 2013;16:554-61.
10. Pothuaud L, Carceller P, Hans D. Correlations between grey-level variations in 2D projection images (TBS) and 3D microarchitecture: applications in the study of human trabecular bone microarchitecture. Bone. 2008;42:775-87.
11. Lewiecki EM, Gordon CM, Baim S, Leonard MB, Bishop NJ, Bianchi ML, et al. International Society for Clinical Densitometry 2007 adult and pediatric official positions. Bone 2008;43:1115-21.
12. McCloskey EV, Odén A, Harvey NC, Leslie WD, Hans D, Johansson H, et al. A meta-analysis of trabecular bone score in fracture risk prediction and its relationship to FRAX. J Bone Miner Res 2016;31:940-8.
13. Iki M, Tamaki J, Sato Y, Winzenrieth R, Kagamimori S, Kagawa Y, et al. Age-related normative values of trabecular bone score (TBS) for Japanese women: the Japanese Population-based Osteoporosis (JPOS) study. Osteoporos Int. 2015;26:245-52.
14. Harvey NC, Glüer CC, Binkley N, McCloskey EV, Brandi ML, Cooper C, et al. Trabecular bone score (TBS) as a new complementary approach for osteoporosis evaluation in clinical practice. Bone. 2015;78:216-24.
15. Leslie WD, Krieg MA, Hans D; Manitoba Bone Density Program. Clinical factors associated with trabecular bone score. J Clin Densitom. 2013;16: 374-379.
16. Rolvien T, Stürznickel J, Schmidt FN, Butscheidt S, Schmidt T, Busse B, et al. Comparison of Bone Microarchitecture Between Adult Osteogenesis Imperfecta and Early-Onset Osteoporosis. Calcif Tissue Int. 2018;103:512-521.
17. Nijhuis WH, Eastwood DM, Allgrove J, Hvid I, Weinans HH, Bank RA, et al. Current concepts in osteogenesis imperfecta: bone structure, biomechanics and medical management. J Child Orthop. 2019;13:1-11.
18. Folkestad L, Hald JD, Hansen S, Gram J, Langdahl B, Abrahamsen B, et al. Bone geometry, density, and microarchitecture in the distal radius and tibia in adults with osteogenesis imperfecta type I assessed by high-resolution pQCT. J Bone Miner Res. 2012;27:1405-12.