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Original article

Low trabecular bone score in adolescent female inpatients with anorexia nervosa

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SUMMARY

Background & aims: Trabecular bone score (TBS) is an emerging technology that provides information regarding bone microarchitecture. A recent study showed that in healthy girls normal TBS (≥1.35) was achieved within the first year post-menarche. The aims of our study was to assess TBS in adolescents with anorexia nervosa (AN) and to evaluate correlations with clinical, laboratory and densitometric variables.

Methods: A cohort study of 208 adolescent females (mean age 15.6 ± 1.8 y) hospitalized because of AN between 2003 and 2017 was retrospectively assessed. Demographic and clinical data, including age, weight, height, body mass index (BMI), laboratory parameters and bone mineral density (BMD) measurements by dual-energy X-ray absorptiometry (DXA) were retrieved from the medical charts. Bone mineral apparent density (BMAD) was calculated for each participant. TBS was assessed by reanalyzing DXA spinal images.

Results: Mean TBS was 1.308 ± 0.083, lower than the values previously described in healthy adolescents ($p < 0.001$). Compromised microarchitecture was found in 17 participants (8.2%) and partially compromised in 123 (59.1%). TBS was significantly correlated with age, weight standard deviation score (SDS), BMI SDS, BMD measurements of the lumbar spine and total body, BMAD, BMAD Z-score, luteinizing hormone (LH) and 17b-estradiol (E2) level, and was negatively correlated with cortisol ($p = 0.017$). Participants with regular menstruation or secondary amenorrhea had higher TBS than participants who were pre-menarche or with primary amenorrhea ($p < 0.001$). A stepwise linear regression analysis identified BMD L1-4 Z-score and log E2 as independent predictors of TBS.

Conclusion: TBS of adolescent females with AN was found to be lower than TBS of healthy adolescents. Prospective longitudinal studies should be undertaken to investigate whether recovery may result in correction of bone microarchitecture.

1. Introduction

Adolescents with anorexia nervosa (AN) exhibit suboptimal bone accretion, skeletal losses [1,2], and a significantly higher risk of fractures compared to healthy controls [3]. Bone mineral density (BMD) as measured by dual-energy X-ray absorptiometry (DXA) is a major determinant of bone strength and fracture risk [4]. However, many individuals with fragility fractures have BMD above the osteoporosis range [5]. This is partially attributable to the fact that impaired bone microarchitecture, independent of BMD, is associated with fragility fractures [6]. In fact, BMD explains only 60–80%

List of abbreviations: anorexia nervosa, AN; bone mineral density, BMD; dual energy x-ray absorptiometry, DXA; Body mass index, BMI; Trabecular bone score, TBS; 25-hydroxy vitamin D, 25OHD; follicle stimulating hormone, FSH; luteinizing hormone, LH; 17b-estradiol, E2; Thyrotropin, TSH; free triiodothyronine, FT3; free thyroxine, FT4; total body less head, TBLH; bone mineral apparent density, BMAD.

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of bone strength, and a number of other skeletal features such as macro-geometry of the cortical bone, trabecular bone micro-architecture, bone micro-damage, bone mineralization and bone turnover contribute to overall bone strength and fracture risk [7,8].

Trabecular bone score (TBS) is a textural index evaluating gray-level textural variations from 1 pixel to the adjusted pixels in the lumbar spine DXA image, providing skeletal information complementary to the standard BMD results [9]. TBS is not a direct measurement of trabecular microarchitecture but it is related to three dimensional bone characteristics such as the trabecular number and trabecular separation [10]. Higher values of TBS are obtained in more homogeneously textured bone, while less well-textured bone results in lower TBS values [5]. TBS score $\geq$1.350 in post-menopausal women is considered normal, whereas values between 1.200 and 1.350 correspond to a partially degraded micro-architecture, and TBS$\leq$1.200 corresponds to degraded microarchitecture [7]. This score has been shown to be a significant predictor of osteoporotic fractures in adult men and women, independently of both BMD and major clinical risk factors [10–12]. A recent study showed that incorporating TBS in the Fracture Risk assessment tool (FRAX) led to an improvement in fracture risk classification and was most effective in women close to an intervention threshold from the traditional assessment and in women younger than 65 years [13].

To date, only a few studies evaluated TBS in the pediatric population [14–17]. A recent study has shown that in a healthy cohort of adolescent girls, normal TBS ($\geq$1.350) was already achieved within the first year following menarche [14]. Thus, TBS may be a useful tool for the evaluation of bone microarchitecture during adolescence.

To the best of our knowledge, only one previous study investigated TBS in AN patients, showing evidence of compromised or partially compromised microarchitecture in 44% of the cohort, and a correlation of TBS with age, height, weight, BMI, pubertal stage, and BMD [16].

The aim of our study was to determine TBS in a large cohort of inpatients adolescent girls with severe AN, and to evaluate the associations with clinical, anthropometric and densitometric variables.

We hypothesized that a significant proportion of our patients will show evidence of compromised microarchitecture, and that TBS will be associated with disease severity.

2. Materials and methods

2.1. Patients

All adolescent females aged 10–19 years diagnosed with AN who were hospitalized in the Pediatric Psychosomatic Department of the Edmond and Lily Safra Children's Hospital between 2003 and 2017 and who had BMD measurements available were included in the study. Exclusion criteria were schizophrenic spectrum disorder, bipolar disorder, substance use disorder, organic–brain disorder, mental retardation, and any significant medical or neurological disorder potentially affecting food consumption, weight and bone metabolism (e.g., diabetes mellitus, primary thyroid disorders, or chronic inflammatory diseases). For patients who had more than one hospitalization during the study period, only data from the first hospitalization was used.

Demographic and clinical data, including age, anthropometric measurements, pubertal staging according to criteria of Tanner [18], laboratory data and psychiatric comorbidity were obtained from the patients' medical charts.

Pre-menarche was defined as no menses prior to the hospitalization and age <15 years (still age appropriate), primary amenorrhea was defined as no menses and age >15 years, and secondary amenorrhea was defined as absence of menses for more than three months in adolescents who previously had regular menstrual cycles or six months in adolescents who had irregular menses [19].

The study was approved by the Institutional Review Board at the Sheba Medical Center. Patients and legal guardians, in the case of minors under the age of 18, agreed to participate in the study by signing a written informed consent.

2.2. Diagnostic interviews

The presence of AN and of comorbid psychiatric disorders was established using the Structured Clinical Interview for Axis I DSM-IV Disorders–Version 2.0 (SCID-I I/P, Version 2.0) [20]. The diagnoses were adapted for the DSM-V [21].

2.3. Anthropometric measurements

Standing height was measured to the nearest 0.1 cm, using a wall mounted stadiometer, and body weight was obtained to the nearest 0.1 kg, with the patient wearing a hospital gown and without any footwear. All measurements were taken during the morning hours, using standardized procedures. Body mass index (BMI) was calculated based on the formula: weight (kg)/height $(m)^2$. Height, weight, and BMI standard deviation scores (SDS) were calculated using age and gender-specific growth data (based on the Centers for Disease Control and Prevention's Year 2000 Growth Charts), found adequate also for Israeli youngsters [22].

2.4. Laboratory tests

Blood samples for calcium, phosphate, sodium, alkaline phosphatase, 25-hydroxy vitamin D (25OHD), thyroid function tests, cortisol, prolactin, follicle stimulating hormone (FSH), luteinizing hormone (LH) and 17b-estradiol (E2) were obtained upon admission to the Pediatric Psychosomatic Department as part of the routine care. Samples were obtained between 07:00 and 09:00 AM after an overnight fast.

Serum calcium, phosphate, sodium and alkaline phosphatase were measured using an autoanalyzer (Olympus AU2700, Hamburg, Germany). 25OHD levels were determined using the DiaSorin LIAISON® competitive two-step chemiluminescent immunoassay. Thyrotropin (TSH), free triiodothyronine (FT3) and free thyroxine (FT4) were measured by UniCel™ DxI 800 Access Immunoassay System (Beckman Coulter Inc., Brea, CA, USA). Cortisol, prolactin, FSH, LH and E2 were measured by a chemiluminescent method (Immulite 2000, Diagnostic Products Corporation, Los Angeles, CA, USA).

2.5. Bone mineral density

BMD at the lumbar spine (L1-L4) and total body less head (TBLH) were evaluated during the first month of hospitalization using DXA (Lunar Prodigy; GE Medical Systems, Madison, WI, USA) as part of patients' routine care. BMD was expressed in grams per square centimeter and in terms of Z-scores and was further adjusted to size by calculating lumbar spine bone mineral apparent density (BMAD) using an adapted method of Carter et al. [23]. BMAD Z-scores were calculated using the Lambda-Mu-Sigma (LMS) method, as described by Crabtree et al. [24]. TBS measurements were obtained retrospectively from DXA spinal images using TBS iNsight Software (version 2.1.1.0, Medimaps) after a calibration procedure.

2.6. Data analysis

The initial analysis included estimations of mean, standard deviations (SD), and frequency distribution. Comparisons between subgroups of patients were made using the unpaired *t*-test for continuous variables, and the Pearson chi-square test for categorical variables. Pearson correlation coefficients were calculated to examine the relationship between potential continuous predictors. The values of alkaline phosphatase, FT4, E2, LH and prolactin were transformed to log scale to improve the symmetry of the distribution. Square root transformation of TSH levels was used to achieve normal distribution. Variables significantly associated with TBS were included in regression models to examine independent predictors of TBS. Results were considered significant if the two-sided p-value was <0.05. Calculations were performed using SPSS 23.0, a statistical software package.

3. Results

Two hundreds and eight patients were included in the study. Their clinical and anthropometric characteristics are presented in Table 1. Mean age at the time of BMD measurement was 15.7 ± 1.8 years (range 10–18.6) and duration of illness at that time was 2.2 ± 1.5 years. Seventy two patients (36.2%) had regular menstruation, 27 patients (13.6%) were pre-menarche, 8 patients (4.0%) had primary amenorrhea and 92 patients (46.2%) had secondary amenorrhea. The mean duration between cessation of menstruation and BMD measurement was 10.5 ± 7.4 months. Mean BMI at the time of BMD assessment was 15.9 ± 2.2 kg/m^2, and mean BMI SDS was −2.2 ± 1.2.

One hundred and twelve participants (53.8%) were diagnosed with depressive disorders, 21 (10.1%) with anxiety disorders, 26 (12.5%) with obsessive compulsive disorder and 21 (10.1%) with attention deficit hyperactivity disorder. The patients were not treated with psychotropic medications during the first month of their hospitalization, at the time when the DXA was performed.

Laboratory results on admission are presented in Table 2. The patients had normal levels of calcium and phosphorus but a relatively low level of alkaline phosphatase (88.6 ± 49.2 IU/l). Vitamin D level was 22.4 ± 6.9 ng/ml.

Mean lumbar spine TBS of the patients was 1.308 ± 0.083, significantly lower than the mean TBS of two previous cohorts of healthy adolescent girls (1.370 ± 0.099 and 1.495 ± 0.054, $p < 0.0001$) [14,15] (Table 3). This finding was observed across all ages (Table 4, Fig. 1) [17]. Seventeen participants had TBS≤1.2 (8.2%), 123 participants (59.1%) had TBS between 1.2 and 1.35 and only 68 (32.7%) had TBS≥1.35.

TBS positively correlated with age ($r = 0.197$, $p = 0.004$), weight SDS ($r = 0.329$, $p < 0.001$), BMI SDS ($r = 0.434$, $p < 0.001$), lumbar spine BMD ($r = 0.541$, $p < 0.001$), lumbar spine BMD Z-score ($r = 0.435$, $p < 0.001$), TBLH BMD ($r = 0.397$, $p < 0.001$) TBLH BMD Z-score ($r = 0.288$, $p = 0.01$), BMAD ($r = 0.52$, $p < 0.001$), and BMAD Z-score ($r = 0.47$, $p < 0.001$). TBS was also positively correlated with E2 ($r = 0.291$, $p < 0.001$) and LH levels ($r = 0.253$, $p < 0.001$) and negatively correlated with cortisol levels ($r = -0.192$, $p = 0.017$).

We further found associations between TBS and pubertal stage. Mean TBS of pre-pubertal participants was 1.159 ± 0.051, of early-pubertal participants (Tanner stage II–III) was 1.259 ± 0.067 and of more advanced participants (Tanner IV–V) was 1.321 ± 0.078. TBS of early-pubertal participants (Tanner stage II–III) was significantly lower compared to the more advanced participants (Tanner IV–V) ($p = 0.002$). Participants who had regular menstruation or secondary amenorrhea had higher TBS than participants who were pre-menarche or had primary amenorrhea ($p < 0.001$, see Table 5).

A stepwise linear regression analysis was used to identify independent predictors of TBS. BMD L1-4 Z-score ($p = 0.023$) and log E2 ($p = 0.001$) were found as significant independent predictors of TBS.

Last, no associations were found between TBS and duration of AN, duration of amenorrhea, and calcium, phosphate, 25OHD, and prolactin levels, (results not shown).

Table 1
Clinical data, anthropometric measurements and BMD parameters of 208 adolescent female inpatients diagnosed with anorexia nervosa.

Variables	Mean ± SD
Age, years	15.7 ± 1.8
Age at menarche, years	12.7 ± 1.6
Duration of AN, years	2.2 ± 1.5
Duration of secondary amenorrhea, months	10.5 ± 7.4
Duration of inpatient treatment, months	5.9 ± 3.1
Tanner stages (n, %)	
I	4 (2.1%)
II–III	17 (8.8%)
IV–V	173 (89.1%)
Anthropometric measurements	
Height, cm	158.5 ± 7.4
Height SDS	−0.36 ± 0.9
Weight, kg	40.26 ± 6.4
Weight SDS	−1.96 ± 1.1
BMI, kg/m^2	15.9 ± 2.2
BMI SDS	−2.2 ± 1.2
Bone mineral density	
Lumbar spine, g/cm^2	0.97 ± 0.14
Lumbar spine Z-score	−1.33 ± 1.21
Total body less head, g/cm^2	1.02 ± 0.09
Total body less head Z-score	−0.52 ± 0.83
Lumbar spine BMAD, g/cm^3	0.285 ± 0.036
Lumbar spine BMAD Z-score	−1.13 ± 1.25
TBS L1-4	1.308 ± 0.083

TBS-trabecular bone score, AN-anorexia nervosa, BMI-body mass index, SDS-standard deviation scores, BMD-bone mineral density, BMAD - bone mineral apparent density.

Table 2
Laboratory data of the 208 inpatients with AN on admission.

Variables	Mean ± SD	Reference range
Sodium, meq/l	138.9 ± 2.0	136–145
Calcium, mg/dl	10.1 ± 0.4	8.1–10.4
Phosphate, mg/dl	4.3 ± 0.5	Age 12–15 years 2.9–5.4
		Age 16–19 years 2.7–4.7
ALP, IU/L	88.6 ± 49.2	Age 12–13 years 105–420
		Age 14–15 years 70–230
		Age 16–19 years 50–130
25OHD, ng/ml	22.4 ± 6.9	>20 ng/ml[a]
Free T3, pmol/l	4.5 ± 0.9	3.8–6.0
Free T4, pmol/l	11.0 ± 3.0	7.0–16.0
TSH, mIU/l	1.9 ± 1.1	0.4–4.0
17b-Estradiol, pmol/l	159.4 ± 216.2	Follicular phase 73-308
		Ovulatory phase 124-1468
		Luteal phase 101-905
FSH, IU/L	5.1 ± 3.2	Follicular phase 2.8-11.3
		Ovulatory phase 5.8-21
		Luteal phase 1.2-9
LH, IU/L	4.8 ± 5.6	Follicular phase 1.1-11.6
		Ovulatory phase 17-77
		Luteal phase 1-14.7
Cortisol, nmol/l	588.7 ± 157.7	138–690
Prolactin, mcg/l	23.8 ± 17.6	0–20

AN-anorexia nervosa, ALP-alkaline phosphatase, 25OHD-25 hydroxy vitamin D, TSH-thyroid stimulating hormone; T4-thyroxine; T3-triiodthyronine; FSH-follicular stimulating hormone; LH-luteinizing hormone.

[a] The recommendation for 25OH-vitamin D levels of the Lawson Wilkins Pediatric Endocrine Society and the IOM.

Table 3
Summary of TBS studies in the pediatric population.

Citation	Population	Ethnicity	Age, years	TBS	Densitometer	Remarks
			Mean ± SD, range	Mean ± SD		
Shawwa et al., 2016 [15]	170 boys	Lebanon	13.0 ± 1.9 (10–17)	1.345 ± 0.095	Hologic 4500A, Bedford MA; software version 11.2:3	Healthy students recruited from 4 schools.
	168 girls		13.2 ± 2.1 (10–17)	1.370 ± 0.019		Raw measurement of TBS.
Dowthwaite et al., 2017 [14]	44 post-menarcheal girls	USA 93% white	12.7 ± 0.6 (11.2–13.7)	1.495 ± 0.054 (raw) 1.497 ± 0.055 (corr)	GE Lunar iDXA, Madison WI	Healthy students recruited from school. Raw measurement of TBS and pediatric soft tissue-corrected TBS.
Del Rio et al., 2014 [17]	1468 boys 2659 girls	Spain	Birth-19 years	Girls >10 years: 1.353–1.489	Prodigy, GE Lunar, USA	Healthy children
Donaldson et al., 2015 [16]	57 girls with AN	USA 81% white	15.5 ± 1.9 (11–18)	1.359 ± 0.100	Hologic, Discovery W; software version 23.1	Recruited from eating disorder program. Adult TBS software was used.
Current study, 2017	208 girls with AN	Israel	15.7 ± 1.8 (10–19)	1.308 ± 0.083	Lunar Prodigy; GE Medical Systems, Madison, WI, USA	Inpatients recruited during hospitalization. Adult TBS software was used.

TBS-trabecular bone score.

Table 4
TBS (mean ± SD) of AN patients in the current study compared to healthy adolescent females.

Age	TBS of adolescent females with AN	TBS of healthy adolescent females [17]	p-value
11–12	1.225 ± 0.053	1.413 ± 0.123	<0.001
12–13	1.261 ± 0.091	1.431 ± 0.135	<0.001
13–14	1.324 ± 0.097	1.471 ± 0.121	<0.001
14–15	1.299 ± 0.094	1.474 ± 0.125	<0.001
15–16	1.326 ± 0.078	1.479 ± 0.112	<0.001
16–17	1.311 ± 0.086	1.473 ± 0.112	<0.001
17–18	1.311 ± 0.067	1.489 ± 0.118	<0.001
18–19	1.332 ± 0.039	1.483 ± 0.099	<0.001

AN-anorexia nervosa.

4. Discussion

Decreased bone density is a common complication of AN [2]. In accordance with multiple previous studies, we demonstrated low bone density in our cohort of AN patients with decreased BMD and BMAD Z-scores. Consistently, we observed low alkaline phosphatase levels, reflecting a low bone turnover state.

In keeping with our hypothesis, we found evidence of suboptimal microarchitecture in more than two thirds of female adolescent inpatients with AN. TBS significantly correlated with age, weight SDS, BMI SDS, BMD measurements, menstruation status, and E2 and LH levels. TBS was negatively correlated with cortisol levels. A stepwise linear regression analysis identified BMD L1-4 Z-score and log E2 as independent predictors of TBS.

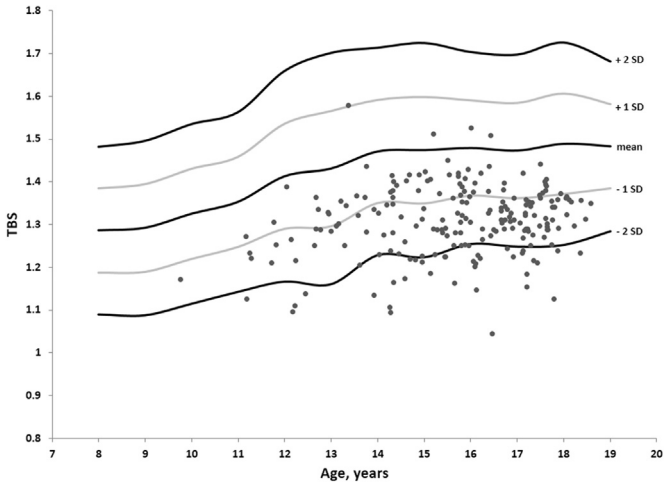

Fig. 1. TBS measurements of 208 AN patients compared to TBS distribution according to age from a large cohort [17]. Dots represent data from our cohort, lines represent data from healthy pediatric population.

To date, few studies evaluated TBS in healthy pediatric populations (Table 3). In a cross-sectional study, Shawwa et al. evaluated TBS in 168 Lebanese girls aged 10–17 (mean age 13.2 ± 2.1) [15]. Mean raw TBS was 1.370 ± 0.099. Similar to our findings in AN patients, post menarcheal girls had significantly higher mean TBS compared to premenarchal girls (1.389 vs. 1.293, $p < 0.001$). Several predictors of TBS were found including: age, pubertal stage, weight, height, BMI, bone mineral content (BMC) and BMD. On multivariate analysis, spine BMC and age remained independent predictors of TBS in girls [15].

Another study assessed the TBS of 44 healthy post-menarche American girls aged 11–13 years (mean age 12.7 ± 0.6 years, menarcheal age 12.2 ± 0.5 years) to evaluate TBS during the first year post-menarche [14]. Raw TBS was 1.495 ± 0.054 (range 1.362–1.577), while pediatric soft tissue-corrected TBS was 1.497 ± 0.055 (range 1.352–1.586). In this study, adult normal TBS (≥1.350) values were achieved within the first year post-menarche, providing a potential screening tool, independent from bone density [14].

In our cohort of adolescent females with AN, mean TBS was significantly lower than the mean scores in both of the above studies, even though the participants in our cohort were older (mean age 15.5 ± 1.9 vs. 13.2 ± 2.1 and 12.7 ± 0.6) (Table 3). This finding may, likely, reflect the deteriorative effect of AN on bone microarchitecture.

TBS is an age-dependent variable [10], as shown also in our study. Similarly, in a study by Del Rio et al. including 4127 healthy children (2659 females and 1468 males) between birth and 19 years, TBS increased with age and reached a plateau at the of age 13

Table 5
TBS of the 208 AN participants according to menstruation status.

Sub-group	N (%)	TBS mean ± SD[a]	BMD L1-4 Z score mean ± SD[b]
Pre-menarche	27 (13.6%)	1.229 ± 0.079	−1.324 ± 0.903
Primary amenorrhea (age>15 years with no menses)	8 (4.0%)	1.265 ± 0.079	−3.163 ± 1.000
Secondary amenorrhea	92 (46.2%)	1.321 ± 0.070	−1.324 ± 0.903
Regular menstruation	72 (36.2%)	1.325 ± 0.079	−1.183 ± 1.251

AN-anorexia nervosa, TBS-trabecular bone score, BMD-bone mineral density.
[a] TBS of participants who had regular menstruation or secondary amenorrhea was significantly higher than TBS of participants who were pre-menarche or had primary amenorrhea ($p < 0.0001$).
[b] BMD L1-4 Z-score of participants who had primary amenorrhea was significantly lower than the other subgroups ($p < 0.0001$).

years in girls [17]. TBS measurements of our cohort were considerably lower than TBS values observed in this study (Table 4, Fig. 1).

The use of TBS in adolescents with AN was assessed for the first time by Donaldson et al. [16]. Fifty-seven participants were recruited from an urban eating disorder program and were in similar ages to our cohort (mean age 15.5 ± 1.9 vs. 15.7 ± 1.8). In this study 44% of the patients had low TBS (<1.350) [16], in comparison to 67.3% in our sample. This difference is likely associated with the severity of the AN that required hospitalization of our participants and with the considerably longer duration of illness in our cohort (mean of 2.2 years vs. 4 months, respectively). In accordance with the greater severity of AN in our cohort in comparison to Donaldson et al. [12], mean BMI (15.9 ± 2.2 kg/m^2 vs. 18.9 ± 1.8 kg/m^2) and mean lumbar spine Z-score (−1.33 ± 1.21 vs. −0.45 ± 1.31), were also considerably lower in our participants. Both studies found significant correlations between TBS and age, weight, BMI, pubertal status and BMD measurements.

Some limitations of the study should be acknowledged. We did not include a control group of healthy girls, comparing TBS measurements of our cohort to findings of previous pediatric studies Secondly, many of our patients had BMI below 15 kg/m^2, while according to the manufacturer's recommendation, TBS measurement is optimized for adults with BMI between 15 and 37 kg/m^2. Raw TBS values may be underestimated if there is excessive soft tissue in the abdomen, overlying the region of interest. Therefore, TBS is adjusted to the patient's BMI as a surrogate of tissue thickness [7]. Previous pediatric studies have used adult TBS software as we did [16], raw TBS data [15] or both raw and pediatric corrected TBS [14]. Nonetheless, our study has some important advantages, mainly the inclusion of a large cohort of patients with more severe disease of longer duration and the ability to assess TBS against important clinical and laboratory parameters.

In conclusion, our study contributes to the growing body of knowledge regarding TBS use in adolescents in general, and is complementary to the previous findings in adolescent patients with AN. TBS reflects bone microarchitecture and may provide a useful tool for assessing bone status of children and adolescents at risk for bone fragility. Future studies should be carried out to provide information whether low TBS during adolescence is predictive for increased fracture risk during adulthood. In addition, this novel technology should be explored in other chronic childhood diseases that affect bone health. In patients with AN, prospective longitudinal studies should be undertaken from the early onset to investigate whether recovery may result in correction of compromised microarchitecture associated with AN-related malnutrition.

Conflict of interest

none.

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