Bone Microarchitecture Assessed by Trabecular Bone Score Is Independent of Mobility Level or Height in Pediatric Patients with Cerebral Palsy

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ABSTRACT
Bone strength and fracture risk do not only depend on bone density, but also on bone structure. The trabecular bone score (TBS) evaluates homogeneity of bone microarchitecture indirectly by measuring gray-level variations of two-dimensional (2D) DXA images. Although TBS is well-established for adults, there have been only few publications in pediatrics. In this monocentric retrospective analysis, we investigated TBS in children and adolescents with cerebral palsy (CP), a patient group vulnerable to low bone mineral mass due to impaired mobility. The influence of different parameters on TBS and areal BMD (aBMD) were evaluated, as well as the relationship between TBS and aBMD. We compared TBS values of our study population to a reference population. A total of 472 lumbar spine–dual-energy X-ray absorptiometry (LS-DXA) scans of children and adolescents with CP (205 female), aged between 4 and 18 years, were analyzed. The DXA-scans were part of the routine examination. The children had no records of fractures or specific bone diseases. Our study population with CP had similar TBS as the reference population. TBS did not increase with age until an inflection point at 10 years in females, and 12 years in males. Girls had significantly higher TBS than boys (p = .049) and pubertal girls aged 8 to 13 years had significantly higher TBS than prepubertal girls (p = .009). TBS standard deviation score for age (SDS-TBS) and aBMD Z-scores correlated weakly (p < .001; R = 0.276 [males], R = 0.284 [females]). Other than for aBMD Z-scores, SDS-TBS was not influenced by age-adjusted height Z-scores and there was no significant difference in SDS-TBS when grouped by mobility levels, using the Gross Motor Function Classification System (GMFCS). Our results indicate that children with CP have a similar homogeneous distribution of trabecular microarchitecture as controls. Puberty initiation appears to be essential for increase of TBS with age and for sex differences. TBS seems less influenced by body composition, height, and mobility than aBMD. © 2020 The Authors. Journal of Bone and Mineral Research published by American Society for Bone and Mineral Research.

KEY WORDS: ANALYSIS/QUANTITATION OF BONE, DXA; BONE-MUSCLE INTERACTIONS; OSTEOPOROSIS; SCREENING

Introduction
With a prevalence of 2 to 3.5 per 1000 live births,1 cerebral palsy (CP) represents the most common syndrome of motor impairment among young children.2 CP is caused by a nonprogressive lesion in the developing fetal or infant brain and encompasses a large and heterogeneous group of motor function disorders. Patterns of motor involvement can include unilateral or bilateral spasticity, dystonia or choreoathetosis, ataxia, or a combination of these symptoms, leading to different

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grades of movement or postural disability and dependency on splints, walking aids, or a wheelchair. Posture and movement disorders are frequently accompanied by other comorbidities, such as cognition, behavior or communication disorders, epilepsy, and secondary musculoskeletal problems.\(^1,2\)

Bone health of children with CP is a challenging issue for the treating clinicians. Because of reduced mobility, children and adolescents with CP are prone to low bone mineral mass and consequently to fragility fractures.\(^3\) Ideally, those individuals at high risk for fractures should be identified before a fracture occurs, so eligible strategies to improve bone strength can be evaluated in order to prevent pain, further immobilization, and deterioration of quality of life.

Areal bone mineral density (aBMD), assessed by dual-energy X-ray absorptiometry (DXA), is commonly used for evaluation of bone mineral mass. Based on a two-dimensional (2D) projection image, aBMD reflects the degree to which radiation is attenuated by bone tissue.\(^4\) It does not take into account the bone's thickness and is therefore only an estimation of a bone's true physical density (mass per volume).\(^4\) aBMD can be measured at different regions of interest like the lumbar spine (LS), the femur or the forearm and age-adjusted Z-scores can be calculated based on reference values. DXA evaluation is recommended by the American Academy for Cerebral Palsy and Developmental Medicine (AACPDM) for children with CP that have a fracture history and/or bone pain, if the patient's clinical management would be influenced by the results.\(^5\) Also, the International Society of Clinical Densitometry (ISCD) considered DXA assessment useful for fracture risk estimation and evaluation of intervention effects in children with CP.\(^5\)

However, an accurate interpretation of aBMD can be difficult. Especially, children and adolescents with severe CP showed low age-adjusted aBMD Z-scores.\(^6–8\) But the reported prevalence of low aBMD is much higher than actual fracture rates.\(^9–10\) aBMD is influenced by various factors, such as height, weight, mobility or anticonvulsant medication.\(^9,7,10\) Compared to typically developing peers, children and adolescents with CP are often smaller, show reduced mobility, lower BMI, and frequently have anticonvulsant therapy or other interfering conditions. These might be reasons for the elevated number of low aBMD in this patient group. Especially, the height dependency is a considerable factor in a population that is growing. Duran and colleagues\(^11\) recently proposed nomograms for an adjustment of aBMD in order to prevent pain, further immobilization, and deterioration of quality of life.

In trabecular remodeling, the BMUs move parallel to the trabecular surfaces.\(^12\) The primary spongiosa, consisting of trabeculae with a core of mineralized cartilage, is replaced by lamellar bone through remodeling.\(^17\) Trabecular bone has a very high rate of bone turnover. The remodeling balance, which describes the difference of resorbed and newly deposited bone tissue, is usually close to zero. Indeed, if less bone is generated than resorbed, the amount and thickness of trabeculae decrease, which results in deteriorated bone microarchitecture.\(^17\)

In modeling, bone resorption and deposition are uncoupled. Osteoblasts and osteoclasts work independently from each other on separate locations of preexisting bone.\(^19\) Cortical thickness, which determines bone mass, increases through modeling on the periosteal surface of the cortex (periosteal appositional bone growth).\(^4\)

Changes of mechanical conditions lead to drifting of trabeculae and cortices by modeling as a functional adaption to load. The trabecular microarchitecture in the spongiosa is dependent on both remodeling and modeling activity.\(^19\)

Standard DXA scans do not analyze bone structure, nor differentiate between the cortical and trabecular bone compartment. pQCT, MRI, or histological studies can give evidence about these parameters but are not suitable as standard procedures because of high costs, radiation exposure, invasiveness, and limited availability.

The trabecular bone score (TBS) is a texture parameter related to bone structure. Based on experimental varigrams, TBS evaluates pixel-to-pixel gray-level variations (ie, heterogeneity of gray-level distribution) in the 2D DXA image. These variations reflect the anteroposterior (AP) projected structure of the vertebral body. Thereby, TBS determines the homogeneity of trabecular microarchitecture indirectly.\(^17\) More homogeneous bone structure shows fewer contrasts in the DXA image and results in higher TBS, whereas porous microarchitecture is reflected in lower values. As such, two DXA scans with similar aBMD can exhibit different TBS values due to different distribution of bone material.\(^20\) It has been demonstrated in ex vivo studies, that TBS significantly correlates with some three-dimensional (3D) bone microarchitecture parameters, such as the trabecular number, bone fractional volume, and connectivity density.\(^21,22\) Because the standard DXA measurement is used and no additional examination is needed, TBS represents a convenient method to obtain additional information on bone microarchitecture.

The use of TBS is well established among adults. TBS is an independent clinical risk factor for osteoporotic fractures in adults and the combination of TBS and aBMD improves risk prediction significantly.\(^11,23,24\) International scientific societies recommend TBS in the management of adult osteoporosis.\(^11,25,26\)
To determine whether TBS provides additional information to bone health assessment in this patient group.

Patients and Methods

Study population

In this monocentric retrospective analysis, 472 LS-DXA scans (L₁–L₄) of children and adolescents with CP were reevaluated for TBS assessment. The study design and population were similar to a recent publication of Duran et al., which focused on the evaluation of LS-aBMD of patients of the same data base. DXA scans were performed among the participants of the rehabilitation program “Auf die Beine” (“On your feet”) at the Center of Prevention and Rehabilitation (University of Cologne, Germany) between 2006 and 2016. The rehabilitation program has been described. The DXA scans were performed as part of the routine examination before the first intervention among the participants of 4 years and older.

The patients’ legal representatives gave their written informed consent for data analysis. The obtained data are stored in a prospective monocentric patient registry, which was approved by the Ethics Committee of the University of Cologne (16-269). This registry is described in detail at http://www.germanctr.de (DRKS00011331), a primary register of the International Clinical Trials Registry Platform of the World Health Organization.

LS-DXA scans of children and adolescents of white ethnicity between 4 and 18 years, with diagnosed CP, were included in the analysis. Exclusion criteria were: history of fractures, additional diagnosis of any specific bone disease, genetic syndromes or chronic diseases with stunted growth, eg, renal failure, and growth hormone or corticosteroid medication. The exclusion criteria were evaluated retrospectively based on patient records. Of 614 scans that met the inclusion criteria, 142 measurements were excluded due to: non-evaluable measurements because of artifacts (88 scans), additional diagnosis, eg, corticosteroid or growth hormone medication (30 scans), and missing TBS calculation due to technical reasons (24 scans). None of the patients had any record of previous fractures and therefore no patient was excluded based on this exclusion criterion. Hence, 472 scans remained for statistical analysis.

Anthropometry and other variables

Height was measured in a standing position using a stadiometer (SECA®, model no. 213; seca GmbH & Co. KG, Hamburg, Germany) in 0.1-cm increments, when children were able to stand. An extendable metal tape was used (Kingsize M®, Weiss Meßwerkzeuge GmbH, Erbendorf, Germany) in children who were unable to stand. Body weight was assessed by a digital scale in 0.1-kg increments. BMI was calculated as the patient’s weight in kilograms divided by the square of the patient’s body length in meters (kg/m²). Height for age Z-scores (HAZ) and BMI for age Z-scores (BAZ) were calculated with gender-specific growth charts for Germany.

The Gross Motor Function Classification System (GMFCS) was used to classify the patients’ mobility level. GMFCS is an age-adjusted five-level classification: patients of level I and II are able to walk independently, whereas those classified as level III to V need assistive mobility devices. For the evaluation of the impact of limited mobility on TBS, the study population was divided into the subgroups mild CP (GMFCS levels I-II) and moderate to severe CP (GMFCS levels III-V), as it is common in literature. In accordance with the criteria of the Surveillance of Cerebral Palsy in Europe, CP subtypes were classified as spastic unilateral, spastic bilateral, dyskinetic, ataxic, and mixed type.

The parents or caregiver were asked about the patient’s pubertal status, distinguishing between “prepubertal” and “pubertal.” These estimations were used to test TBS differences between prepubertal and pubertal patients, in order to avoid age bias, only subjects within the age ranges of the physiological onset of puberty (9 to 14 years in boys and 8 to 13 years in girls) were included in this analysis.

DXA and TBS measurement

LS-DXA scans were performed using Prodigy Advance® (01/2006–03/2011) or iDXA (04/2011–09/2016; both from GE Healthcare, Buckinghamshire, UK) with the Encore® software versions 10 to 14. To unify for algorithm version and acquisition mode, the raw data of every measurement was recalculated with the same, then most recent Encore software version 14.1 on iDXA. Quality control assurance measurements were performed in accordance with the manufacturer’s recommendations. Precision for LS-aBMD in children was reported in literature with 0.31% coefficient of variation. Three trained examiners with long-time experience conducted the measurements. Clothing of the patients and positioning on the device were executed as instructed by the manufacturer. Owing to the available reference data, the software calculated LS-aBMD Z-scores only for children age 5 years and older.

TBS was computed from the LS-DXA images by a custom version of TBS iNsight (Medimaps SASU, Mérignac, France). The calculated raw TBS was adjusted with a calibration equation, based on phantom scans with dedicated calibration phantoms. Corrections for acquisition mode and inter-brand variability were carried out. In addition, a dedicated soft tissue correction was applied, based on patients’ tissue thickness instead of BMI. These corrections were provided by the manufacturer, by means of ex vivo vertebrae and a soft tissue kit with a thickness varying from 9 to 30 cm. This modification compensates technical
acquisition effects (increase of image noise) linked to increased soft tissue.

TBS reference values

At the World Congress on Osteoporosis, Osteoarthritis and Musculoskeletal Diseases 2014, Del Rio and colleagues\(^\text{34}\) presented TBS data of 4127 healthy, typically developing children of a Spanish population group. These data included mean TBS values for age of 2659 girls and 1468 boys, aged between birth and 19 years. We used these mean TBS values as reference values and calculated a standard deviation score (SDS). TBS for age (SDS-TBS) was calculated as: SDS-TBS = (TBS-TBSnorm)/SDnorm. SDS-TBS was used for further correlation analysis, in order to avoid age bias.

Statistics

IBM SPSS Statistics for macOS, version 25 (IBM Corp, Armonk, NY, USA) was used for statistical data analysis. Data distribution was explored by the Shapiro-Wilk test and Q-Q plots. For comparison of subgroup means, t test statistics were assessed for normally distributed data and Mann-Whitney U test was used in non-normally distributed data. Pearson correlation and linear regression analysis were used to explore the relationship between variables. Values of \(p < .05\) were set as the threshold for statistical significance. Results are presented as mean ± standard deviation (SD) or count (relative frequency), unless otherwise stated.

Results

Baseline demographics

A total of 472 LS-DXA scans of patients with CP were analyzed regarding TBS and LS-aBMD. The study group consisted of 205 females and 267 males. All age groups between 4 and 18 years were represented in both sexes, except for 18-year-old girls. A total of 104 participants were classified as GMFCS levels I-II and 343 as GMFCS levels III-V; information on GMFCS levels were missing in 25 patients. Mean age was 9.26 ± 3.58 years, and mean age-adjusted BMI Z-score (BAZ) was −0.38 ± 1.54, with no significant differences between sexes (\(p = .901\) and \(p = .255\), respectively) or GMFCS subgroups (\(p = .734\) and \(p = .848\), respectively). Mean age-adjusted height Z-score (HAZ) was −1.14 ± 1.29. Females and the subgroup of GMFCS levels III-V had significantly lower HAZ than males and GMFCS levels I-II, respectively (\(p = .022\); \(p < .001\)).

A total of 376 participants had bilateral spastic CP (79.7%), followed by 41 with mixed type (8.7%), 29 with unilateral spastic CP (6.1%), 20 with dystonic (4.2%), and six with ataxic CP (1.3%). Fifty-nine patients (12.5%) had anticonvulsant medication, but there was no significant difference between TBS of patients with and without anticonvulsant medication (\(p = .303\)). The main baseline characteristics are shown in Table 1.

Influence of age, sex and pubertal status on TBS in children with CP

Although LS-aBMD values increased steadily between ages 4 to 18 years, TBS remained nearly constant from 4 to 9 years with similar values in both sexes (Fig. 1). TBS increased with age between 10 to 17 years in girls and from 12 to 18 years in boys. In girls, the inflection point was earlier, and they had higher TBS than boys from that point on.

Overall TBS values were significantly higher in females than in males (\(p = .049\)). Considering the suggested inflection point, sex differences resulted to be of higher significance in the age group 10 to 18 years (\(p = .020\)), whereas there was no significant difference between 4-year-old and 9-year-old males and females, respectively (\(p = .383\)).

Between 8 and 13 years, pubertal girls had significantly higher TBS values (mean TBS 1.332) than prepubertal girls of the same age group (mean TBS 1.268) (\(p = .009\)). There was no significant difference between prepubertal and pubertal boys between 9 and 14 years (\(p = .727\)) (Supplemental Fig. 1).

Comparison to TBS data of typically developing children and adolescents

Comparing our data to Del Rio and colleagues\(^{34}\) data of typically developing children, we observed similar mean TBS values in children and adolescents with CP Fig. 2 (Fig. 2A/B female/male). Girls between 9 and 16 years showed a tendency toward lower TBS values than typically developing girls of the same age, but their mean TBS was still within 1 SD of typically developing girls’ mean TBS, with the exception of 10-year-old girls (mean SDS-TBS −1.102). The SDs of TBS in 10-year-old and 15-year-old girls were wide due to one outlier with low TBS value in each age group.

Mean SDS-TBS of boys with CP was −0.006 ± 1.526 and mean SDS-TBS of girls with CP was −0.384 ± 1.088; 17 boys (6.4%) and 10 girls (4.9%) had SDS-TBS below −2.

### Table 1 Baseline Demographics of the Study Population

| Characteristic | All (n = 472) | Sex | GMFCS level |
|---------------|--------------|-----|-------------|
| Age (years)   | 9.26 ± 3.58  | Male (n = 267) | Female (n = 205) | I–II (n = 104) | III–V (n = 343) |
| Height (cm)   | 127.49 ± 19.29 | 128.17 ± 19.91 | 126.60 ± 18.46  | 129.72 ± 18.55 | 126.59 ± 19.38 |
| Height, Z-score | −1.14 ± 1.29 | −1.02 ± 1.25\* | −1.30 ± 1.32\* | −0.64 ± 1.16\* | −1.28 ± 1.28\* |
| BMI (kg/m²)   | 16.39 ± 3.26  | 16.28 ± 3.27   | 16.53 ± 3.25   | 16.17 ± 2.70   | 16.37 ± 3.29   |
| BMI, Z-score  | −0.38 ± 1.54  | −0.45 ± 1.51\* | −0.28 ± 1.59\* | −0.37 ± 1.36\* | −0.40 ± 1.60\* |
| LS-BMD (g/cm²) | 0.63 ± 0.16  | 0.61 ± 0.14   | 0.67 ± 0.17   | 0.68 ± 0.14   | 0.62 ± 0.16   |
| LS-BMD, Z-score | −1.30 ± 0.99 | −1.41 ± 0.95  | −1.16 ± 1.03  | −0.80 ± 1.01  | −1.47 ± 0.92  |
| TBS L₁–L₄   | 1.30 ± 0.11   | 1.30 ± 0.10   | 1.32 ± 0.11   | 1.31 ± 0.09   | 1.30 ± 0.11   |

All values are mean ± SD. Differences between sexes or GMFCS subgroups are marked as significant (*) or nonsignificant (NS).
Correlations of SDS-TBS with HAZ and BAZ in children with CP

There was no significant correlation between SDS-TBS and age-adjusted HAZ ($p = .510$ for males, $p = .456$ for females). Also, SDS-TBS and age-adjusted BAZ did not correlate in girls ($p = .660$). In boys, there was a weak but significant correlation between SDS-TBS and BAZ ($p = .005$, $R = 0.171$).

LS-aBMD $Z$-scores correlated significantly ($p < .001$) with HAZ ($R = 0.480$ in males; $R = 0.450$ in females) and BAZ ($R = 0.439$ in males; $R = 0.446$ in females) in both sexes. The relationship of SDS-TBS and BMD $Z$-scores with HAZ and BAZ is illustrated in Fig. 3 (Fig. 3A/B TBS female/male, Fig. 3C/D LS-BMD female/male) and Supplemental Fig. 2, respectively.

Correlations of absolute TBS with absolute height in children with CP

Absolute TBS and absolute height show significant, but small correlations ($p = .009$ for males, $p < .001$ for females; $R = 0.159$ in males, $R = 0.258$ in females). LS-aBMD shows strong correlation with absolute height in both sexes ($p < .001$; $R = 0.809$ for males, $R = 0.826$ for females). For comparison with Fig. 3, the relationship of TBS and LS-aBMD in g/cm$^2$ with height in cm is illustrated in Supplemental Fig. 3.

Influence of mobility level on age-adjusted SDS-TBS

There was no significant difference in SDS-TBS between GMFCS levels I-II and III-V ($p = .715$ in males, $p = .055$ in females).

LS-aBMD $Z$-scores were significantly lower in GMFCS levels III-V than in GMFCS levels I-II in both sexes ($p < .001$) (Fig. 4A/B TBS/LS-BMD).

Correlation of TBS and LS-aBMD

There was a weak, but significant correlation between aBMD $Z$-scores and SDS-TBS in both sexes ($p < .001$; $R = 0.274$ in males; $R = 0.284$ in females). Similarly, TBS values correlated weakly with LS-aBMD values in both sexes ($p < .001$; $R = 0.294$ in males; $R = 0.426$ in females).

Discussion

To our knowledge, this is the first study investigating TBS assessment in children and adolescents with CP. A total of 472 TBS measurements were analyzed regarding their relationship with different parameters, and compared to the TBS values for healthy, typically developing children. For comparison, we also evaluated the relationship of LS-aBMD and LS-aBMD $Z$-scores with some of the explored parameters.

We found TBS to stay nearly constant with age until an inflection point, and to increase steadily from that point on until 18 years. This inflection point seems to coincide with the start of puberty, which would explain the earlier rise in girls. Girls had higher overall TBS values than boys, and significance increased when testing in the age group 10 to 18 years. In addition, pubertal girls had significantly higher TBS than prepubertal girls, whereas there was no difference in boys regarding pubertal status. These findings would suggest a strong influence of puberty on the distribution of trabecular bone mass, which seems to be more pronounced in girls. The gender-specific influence on cortical bone area and bone mineral content is well established. On the forearm, boys expand their cortical bone area mainly periosteally during puberty, leading to increased bone strength, whereas in girls endocortical apposition is a
Fig 2 Comparison of mean TBS values ±1SD of children with CP and a healthy, typically developing reference population (data from Del Rio and colleagues (34)). (A) Male, (B) Female.
well-known mechanism in puberty, suspected to serve as calcium supply for pregnancy and lactation.⁴³

Del Rio and colleagues³⁴ found TBS to first decrease until puberty, with a negative peak between 5 and 9 years, and then increase until 17 years. The trend of their data is displayed in Fig. 2, in comparison to our data. The overall trend of our data was similar, although a decrease was less evident in boys, and not evident at all in girls of our study population.

In a Lebanese study population of 338 healthy school children (168 female) aged 10 to 17 years, TBS started to increase from an inflection point at 13 years until 17 years. The trend of their data is displayed in Fig. 2, in comparison to our data. The overall trend of our data was similar, although a decrease was less evident in boys, and not evident at all in girls of our study population.

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Hence, studies investigating the influence of age and puberty on TBS mostly indicate a strong influence of puberty on bone texture, because TBS starts to rise at the age of puberty initiation. As for the variability of chronological age at puberty onset and the wide range of maturation rates, Guagnelli and colleagues³⁰ recently proposed to evaluate TBS in children based on bone age. In their study, a prepubertal decline of TBS values was visible in girls, which disappeared after correction with bone age. This is a valid approach to adjust for puberty but would require additional hand skeletal radiographies of the patients. Bone age was not assessed in our study population. The slight prepubertal decline of TBS visible in boys in our data, might possibly have been ameliorated with correction for bone age.

Nevertheless, similar to our finding, Neu and colleagues⁴⁴ performed pQCT studies of the forearm in children and adolescents, where volumetric bone mineral density of the trabecular bone (vBMD_trab) declined about 10% in boys from age 6 to 7 to age 8 to 9, whereas there was only a slight decline in girls. At least in a healthy population, bone age should be normally distributed. If and why TBS and vBMD_trab is declining in prepubertal boys must be investigated further.

Regarding the age range between 4 years until puberty initiation, no increase of TBS values was observed. Changes of bone size and volume during growth seem to have no influence on TBS during this period.

In comparison to Del Rio and colleagues³⁴ data of typically developing children, our study population with CP had similar mean TBS values, suggesting normally distributed microarchitecture in this patient group. Because none of the children had records of any fractures, the results seem plausible. The tendency of lower TBS values in 9-year-old to 16-year-old girls could possibly be due to a delayed pubertal development in children with CP.⁴⁵

There is a number of publications reporting worse GMFCS levels to be associated with lower aBMD_Z-scores.⁷–¹⁰ Similarly, in our study population, LS-aBMD_Z-scores were significantly

Fig 3 Correlations between SDS-TBS (TBS standard deviation score for age, calculated with data from Del Rio and colleagues’³⁴ reference population) and height Z-scores for age (A, B), and between aBMD_Z-scores for age and height Z-scores for age (C, D). Regression lines are shown only for significant correlation (p < .05).
lower in GMFCS levels III-V than in levels I-II. Lower bone mass in those children with more impaired mobility can be explained by the functional muscle-bone unit. Bone modeling and remodeling, and thereby bone strength, are regulated by the forces applied to the bone, which are mainly skeletal muscle forces. Physical inactivity or muscle function disorders, as present in CP, cause a physiological “disuse-pattern osteopenia.”

Surprisingly, we found no significant difference in SDS-TBS between GMFCS levels I-II and III-V.

Wren and colleagues compared 37 children with CP and 37 children in the control group in a QCT study in respect to differences in volumetric cancellous bone density (vBMD) and cross-sectional area (CSA) in the spine (L3). In CP patients the tibia was also investigated. The bone size of the vertebral body L3 in CP was significantly smaller with decreasing mobility level, but no difference in vBMD was shown \( (p = .49) \). In the tibia, bone size \( (p = .02) \) and vBMD \( (p = .09) \) decreased with increasing GMFCS levels, even after adjusting for weight, height, and sex. These results are in accordance with our results of unaffected SDS-TBS in the spine and the results of the studies of Modlesky and colleagues and Binkley and colleagues.

Henderson and colleagues also found that aBMD is lower in the femur (mean BMD Z-score \(-3.5 \pm 0.2\) ) than in the spine (mean BMD Z-score \(-2.0 \pm 0.1\) ) within the same individuals with CP, though not corrected for height.

The homogeneity of trabecular microarchitecture of the spine in children with CP seems to be maintained, despite reduced mobility. The reason for this pattern might be that the mechanical load in children with CP is more physiological in the spine (eg, sitting, wheelchair), than in the lower extremity. The differences between GMFCS-levels in LS-aBMD could be explained, at least partially, by smaller size of the vertebral bodies.

Recently, Trinh and colleagues published a study investigating TBS assessment in adults with CP \( (n = 43, \text{median age } 25 \text{ years}) \). Contradicting our results, they found patients of GMFCS levels I-III to have significantly higher TBS than GMFCS levels IV-V \( (p = .019) \). Almost 56% (55.8%) of their patients had TBS values indicating intermediate or high risk of fracture, defined as TBS >1.3. Although this will have to be investigated further, the results of the two studies cannot be fully compared, due to differences in the study cohort and exclusion criteria. In general children have, due to growth, a higher remodeling rate, that might compensate the loading differences existing between GMFCS levels. We excluded patients with concomitant medications, known to have effect on bone mineral density (eg, corticosteroids). Additionally, in our cohort there were no patients with history of fractures. Fracture risk levels are not defined for children, and therefore cannot be applied here. Furthermore, we compared patients with GMFCS levels I-II and III-V, whereas Trinh and colleagues compared patients with GMFCS levels I-II and IV-V. In the adult study, there was only a small number of patients in both groups (17 versus 26).

Regarding the correlations between TBS and anthropometric or densitometric parameters, contradictory results can be found in literature. Most studies found significant correlations between TBS and aBMD \( (R = 0.18 \text{ to } 0.49 \text{ in boys, } R = 0.32 \text{ to } 0.81 \text{ in girls}) \), and between TBS and aBMD Z-scores \( (R = 0.44-0.65 \text{ in girls, no data for boys}) \). The relationship between TBS and height or BMI were reported as not significant by some authors, whereas other studies found correlations.

However, none of the studies analyzed correlations between TBS for age (SDS-TBS) and age-adjusted Z-scores for height, BMI, or aBMD. Because TBS shows an overall increase with age, we used SDS-TBS, based on Del Rio and colleagues data, in order to avoid age bias in the analysis. There was no significant correlation between SDS-TBS with HAZ in both sexes. SDS-TBS correlated weakly with BAZ in boys, but not in girls. On the contrary, LS-aBMD Z-scores correlated with HAZ and BAZ, in both sexes. Absolute TBS and SDS-TBS showed a weak correlation with LS-aBMD and LS-aBMD Z-scores, respectively.

These discrepancies in correlations, as well as the weak correlation of TBS (SDS-TBS) with LS-aBMD (LS-aBMD Z-scores), indicate that TBS can contribute additional diagnostic value to the conventional DXA evaluation. Our results suggest for SDS-TBS to be independent of age-adjusted height and BMI Z-scores, and therefore less biased by body composition than aBMD Z-scores.

Height-bias is an especially well-known problem of DXA aBMD. The aBMD measurement does not take into account bone depth, but a larger and deeper bone will absorb more radiation than a smaller bone. Therefore, smaller children will always have lower aBMD than taller children with the same physical bone density. TBS, ie, the measurement of gray level variations in the DXA projection image, in contrast, seems to remain unaffected by an increase of bone volume per projection area.
Consideration of TBS as independent of age-adjusted height and BMI could help to improve the overall evaluation of the DXA measurement.

Further research is needed to assess the value of TBS in children with CP, for instance in studies evaluating treatment effects.

Limitations

Some limitations of this study need to be acknowledged. Inclusion and exclusion criteria were evaluated retrospectively on the base of patients’ records. Asking for medical conditions was part of the patients’ history, but, eg, a fracture, could have been forgotten in individual cases. As for the absence of any fractures in the patients’ records, this study cannot provide data about fracture prediction capabilities of TBS. Also, the evaluation of the pubertal status was an estimation of the caregiver or parent, and therefore not as accurate and differentiated as a physical examination and classification of Tanner stages could be.\(^{40}\)

Finally, the study population consisted of participants of an intensive rehabilitation program and might not be representative of all children with CP and might therefore cause a selection bias.

Conclusions

In summary, our findings indicated that children and adolescents with CP without history of fractures or bone disease have normally homogeneous trabecular microarchitecture of the spine evaluated by TBS, despite reduced mobility. The increase of TBS with age and the sex differences, appear to be mainly driven by the initiation of puberty, with a stronger effect on girls. TBS in CP seems to be more independent than aBMD, regarding the influence of anthropometric parameters and mobility. These results suggested for TBS to provide additional information on bone structure, complementary to the conventional DXA assessment. Given the wide availability of DXA measurements and the easy assessment, there might be potential to add information in pediatric bone health assessment. For routine assessments in pediatrics though, there is need for further investigation, a pediatric software version, as well as published reference values. And above all, the potential of TBS to predict fractures in children and adolescents still needs to be explored.

Disclosures

RW was senior scientist to Medimaps during conducting this investigation. MA, ID, KM, HHK, ES, OS, and MR declare that they have no conflict of interest.

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