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Research Article

Bone Mineral Density and Skeletal Manifestations in Patients with Sotos Syndrome

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Abstract

Objective: Sotos syndrome is a rare overgrowth disorder. Bone mineral density (BMD) and bone turnover data in patients with Sotos syndrome are scarce. We describe the skeletal status of a paediatric cohort and also pursue the best method to adjust bone mineral density for their tall stature.

Patients and methods: Bone mineral density, bone geometry and laboratory metabolic bone profile were measured in children with diagnosis of Sotos syndrome. Dietary and fracture history, skeletal deformities and presence of pain and comorbidities were recorded.

Results: Eighteen patients aged five to eighteen years old were assessed; twelve (67%) had scoliosis. There was no history of fracture or significant bone pain. However, they all had suboptimal dietary calcium intake. Median, unadjusted for body size BMD Z-scores of lumbar spine and total body less head were normal. However, the Z-scores BMD obtained through height-age ("Ht-A") and bone age ("BA") adjustment were lower, especially at the lumbar spine site. Bone markers were within normal values. Regarding bone turnover, a strong negative correlation was found between Z-score BMD TBLH ("BA") and urinary calcium excretion (UCa/Ucr) (r: -0.731, $p<0.05$). Finally, a positive correlation was found between Z-score BMD LS ("BA") and osteocalcin (OC) (r: 0.57, $p<0.05$).

Conclusion: There was no evidence of osteoporosis in our cohort. Bone mineral density adjustment with bone age reflected our cohort's bone profile more effectively than with height-age, as it was correlated significantly with urinary calcium excretion and osteocalcin. Therefore, UCa/Ucr and OC could potentially have a prognostic value for skeletal health.

ABBREVIATIONS

BMD: Bone Mineral Density; TBLH: Total Body Less Head; LS: Lumbar Spine; "Ht-A": Height For Age; BA: Bone Age

INTRODUCTION

Childhood and adolescence are the key periods for bone growth. Bone mineral density (BMD), increases during childhood and it is well known that adolescence is a period of substantial bone accrual, which is crucial for future skeletal health [1]. Sotos syndrome is a rare overgrowth syndrome [2], with an estimated frequency of 1-9/100.000 children, which is characterized by a distinctive facial appearance, learning disability and overgrowth (height and/or head circumference ≥ 2 SD above the mean). It is caused by a mutation in the NSD1 gene [3]. Major features of Sotos syndrome include behavioral disorders, cardiac and renal anomalies, scoliosis, and seizures [3,4].

According to current literature, a long list of chronic diseases can result in suboptimal accrual of skeletal mass [5-11]. On the other hand, exercise during growth increases bone mass and is beneficial for skeletal development [12]. Moreover, it is described that children with autism spectrum disorder (ASD), occasionally follow an unhealthy, restrictive diet and this may lead to nutritional deficiencies [13,14]. Increased prevalence of ASD in patients with Sotos syndrome has already been described [15]. Taking the aforementioned factors into account, patients with Sotos syndrome could be at risk for compromised bone health due to limited physical activity in some cases, diet imbalance especially in children with autistic behavior and possibly unknown intrinsic factors associated with this syndrome. In addition, bone mineral density and current bone turnover data in these patients are scarce.

The aim of this study was to describe the skeletal status of paediatric patients with Sotos syndrome. As tall stature leads to overestimation of bone mineral density according to the official revised positions of the International Society for Clinical Densitometry (ISCD) [16-18], we also aimed to pursue the best method to adjust bone mineral density for bone size: height-age ("Ht-A") vs bone age ("BA"). Finally, we explored whether metabolic bone markers could be of prognostic value for the bone

profile of these patients. Currently there are no relevant data on this genetic disorder, to our knowledge.

MATERIALS AND METHODS STUDY POPULATION

In this cross sectional study, we evaluated Caucasian children and adolescents with clinically and genetically confirmed Sotos syndrome. All patients were recruited from the same referral tertiary paediatric hospital and were examined by an experienced team of a clinical geneticist, a paediatrician specialized in bone and mineral metabolism, a general paediatrician and orthopedists. Inclusion criterion was the diagnosis of Sotos syndrome in children aged five to eighteen years, in order to be able to have a DXA scan (dual-energy X-ray absorptiometry), which is suitable for this age range.

Exclusion criterion was the current use of medications known to affect the skeleton, e.g. systemic corticosteroids. Those patients who had a history of an orthopedic procedure involving metal implants, e.g. spinal fusion were not scanned for BMD assessment; however, their metabolic bone profile (laboratory profile) was performed, along with the clinical assessment.

History and clinical approach

Anthropometric data were recorded, i.e. weight (Wt) and height (Ht), using electronic scales and Harpenden's stadiometer, respectively. Patients were weighed barefoot and after overnight fasting. Body mass index (BMI) was calculated for all patients, using the formula: BMI = Wt (kg)/Ht^2(m^2). The anthropometric data were obtained at the time of BMD measurement. On the basis of sexual maturity rating, our patients were further classified as prepubertal (Tanner stages 1 and 2) or pubertal (Tanner stages 3, 4 and 5).

Skeletal abnormalities, with emphasis to scoliosis, were assessed. We also focused on daily calcium (Ca) intake, using a relevant questionnaire [19]. Fracture history and degree of exercise (exercise other than physical education at school) were also recorded.

Bone assessment

All study participants underwent BMD measurement, assessed with dual-energy X-ray absorptiometry (DXA), which is the preferred tool for evaluating bone mass in both children and adults [16]. On the day of the examination, the patients wore metal-free, light clothing. The DXA software was paediatric (General Electric Lunar Prodigy pediatric edition encore 2008) and its reference data were derived by an Italian reference population and were used for automatic calculation of Z-scores for BMD. Before scanning, the radiologist followed the manufacturer's protocol for calibration of the device, using a proper phantom (daily quality assessment). The coefficient of variation, which reflects measurement precision, was 1.5% for lumbar BMD and 1.1% for subcranial total body BMD. As far as the radiation exposure was concerned, it was less than two mSv, so well below natural backround radiation.

Areal BMD (g/cm^2) was measured at two sites; lumbar spine (L1-L4, LS) and total body less head (TBLH). The results were presented as age- and gender-matched BMD Z-scores arising from the DXA manufacturer. Unadjusted BMD values of lumbar spine (LS, L1-L4) and total body less head, expressed in Z-scores were recorded and were subsequently adjusted according to height for age, when height for age was ≥ 2 SD above the mean of the general population. Height-age was defined as the age at which the child's height was the 50th centile on the growth chart.

Importantly, bone dimension parameters, available by the TBLH scan and expressed as percentiles, were also recorded. These were: height for age (bone length), bone mineral content (BMC) for bone area (bone weight), bone area for height (bone width), lean body mass (LBM) for height (muscle mass, corrected for height), BMC/LBM ratio (proxy for bone strength). Finally, body fat percentage (BF%) was also automatically available by the apparatus and was also evaluated.

A radiograph of the left hand and wrist for bone age was also obtained and was read according to the method of Greulich and Pyle by the pediatric radiologists in our institution. BMD Z-score adjustment according to bone age was then calculated for both sites of measurement. The difference between Z-scores BMD ("un") and Z-scores BMD ("Ht-A" / "BA") were also calculated and was expressed in percentage (%).

Laboratory Parameters

On the day of DXA scan, fasting morning blood and second morning void urine samples were obtained for basic bone profile: calcium, phosphorus, magnesium, alkaline phosphatase (ALP) (standard laboratory methods), parathormone, 25-(OH)-vitD and also for bone turnover markers. Vitamin D (25- (OH)-vitD) and parathormone (PTH) levels were measured, using electro-chemiluminescence immunoassay (ECLIA, Roche Diagnostics International Ltd, Switzerland).

The panel of bone formation markers included: insulin – like growth factor 1 (IGF-1, marker of bone modeling; Immunodiagnostic Systems Ltd, Boldon, Tyre&Wear, UK), osteocalcin (OC, Quidel corporation, San Diego, USA) and procollagen I C-terminal propeptide (PICP, Quidel corporation, San Diego, USA, all measured with enzyme-linked immunoassay (ELISA). For bone resorption, the following markers were determined: urinary deoxypyridinoline/urinary creatinine (DPD/cr, Quidel corporation, San Diego, USA), bone tartrate-resistant acid phosphatase type 5b (bTRAP5b, Immunodiagnostic Systems Ltd, Boldon, Tyne&Wear, UK) and Urine Ca/Cr (atomic absorption spectophotometry, SHIMADZU AA-6800). The aforementioned markers were measured with enzyme- linked immunosorbent assay (ELISA), with the exception of UCa/UCr, which was determined with atomic absorption. Z-scores of the above bone markers were calculated, using local reference values, to allow comparisons between different age groups. IGF-1 was compared to the reference range given by the manufacturer of the kit.

Ethical approval

The study was approved by the Ethical Committee of our institution and is in accordance to the Helsinki Declaration of 1975. Informed consent was obtained from all individual participants included in the study. For this study no healthy children were recruited as controls. The rational for this approach was the avoidance of radiation exposure and also of

venipuncture, which can be a painful and unpleasant procedure. Instead, DXA software control data, as well as reference values from our laboratory were used.

Statistical Analysis

SPSS package version 23.0 was used for our data analysis. Descriptive statistics were done in all subjects and were expressed as median values (minimum, maximum). To allow comparisons between different age groups, growth, DXA and lab parameters were converted to Z-scores, using the formula: Z-score = actual value - mean value/SD, where SD stands for standard deviation. For the comparison of group medians, the student t test and Mann-Whitney U test were used, for normally and abnormally distributed data, respectively. Correlations between bone markers, clinical indices and BMD were calculated using Spearman's method. Statistical significance was defined as $p<0.05$.

Initially for comparisons with the general population we compared all Z-scores available to Z- score=0, assuming that Z-score=0 corresponds to the mean of the general population (50^{th} centile). Our patients were also categorized in the following subgroups: patients with scoliosis vs patients without scoliosis, prepubertal vs pubertal patients and patients with coexisting renal disorder vs patients without renal disorder. Descriptive statistics, expressed as median values (minimum, maximum) were also calculated in these subgroups.

RESULTS

Patient characteristics and anthropometry

A total of eighteen patients with Sotos syndrome, clinically and genetically confirmed, consented to the study (fifteen boys, three girls). The mean age of the participants was 11.5 years (range: 5-17.5 y).

As expected, given that Sotos syndrome is an overgrowth disorder, the median Z-score Ht of our patients was higher in comparison with the general population (Z-score Ht=0). Anthropometric values in Z-scores (Wt, Ht, BMI) and pubertal status are depicted in Table 1.

On examination, all patients had similar musculoskeletal abnormalities such as macrocephaly, long arms and legs, flat feet (pes planovalgus) and genu valgum, whereas twelve out of eighteen patients (67%) had scoliosis. In the patients with scoliosis, median Cobb angle was 13^{o} (range:12^{o}–60^{o}). Two patients had spinal surgery for severe scoliosis (preoperative Cobb angle>40^{o}).

In addition, all patients had suboptimal daily Ca intake for their age (<800-1000mg/24h). Significant pain or low energy fracture was not reported. Ten out of eighteen patients (56%) were on extracurricular exercise.

Renal disorder is a relatively common comorbidity in patients with Sotos syndrome. According to our patient's history, we noticed that eight out of eighteen patients (45%) had one of the following renal disorder: vesicoureteral reflux (2/18), horseshoe kidney (1/18), nephrolithiasis (2/18), solitary kidney (1/18) and dysplastic kidney (2/18). On reviewing their medical files, we found no patients on renal failure.

Bone mineral Density

Regarding BMD TBLH assessment, this site was scanned in twelve patients, due to inability to cooperate in four patients and also to the presence of metal implants in two patients (history of spinal surgery). Median unadjusted Z-score BMD TBLH was higher than median Z-score BMD TBLH adjusted for height-age and median Z-score BMD TBLH adjusted for bone age. The difference in percentile (%) between Z-scores TBLH ("Ht", "BA") and TBLH ("un") was also estimated. The aforementioned data are illustrated in detail in Table 2.

The BMD LS assessment was performed in fifteen patients, as those patients with spinal surgery (n=2) and one with lack of cooperation were excluded. Likewise, median Z-score BMD LS ("un") was higher than median Z-score BMD LS ("Ht-A") and median Z-score BMD LS ("BA"). The difference in percentile (%) between BMD Z-scores LS ("Ht", "BA") and BMD Z-scores LS ("un") was also estimated. These data can be seen in Table 3.

Of note, only one patient had unadjusted BMD Z-score < -2 at both sites of measurement, i.e. low for his chronological age; however, he had no history of fracture, hence a diagnosis of osteoporosis could not be established, based on the existing paediatric definition [16].

Figures A and B provide a pictorial overview of BMD Z-scores at both sites, including unadjusted, corrected for "Ht-A" and corrected for "BA" values. The overestimation of unadjusted BMD for TBLH and LS scans is obvious and shows the importance of interpreting DXA data after proper corrections for body size. Following these corrections, median Z-scores continue to fall within normal range (i.e. between -2 and +2).

Laboratory assessment Basic bone profile

No significant abnormalities were found in the following biochemical markers: Ca, ALP, Mg, P. Median 25-(OH)-vitD was 27.3 ng/ml (range: 14.8-44.9 ng/ml), with only one patient having vitD insufficiency, i.e. <20 ng/ml. He subsequently received 2000

Table 1: Paediatric Sotos population overview.

Variable	Median	Minimum	Maximum	p-value
Z-score Ht	1.75	0.2	4.38	<0.001*
Z-score Wt	0.89	-3.8	3.5	0.56
Z-score BMI	0	-2	2.2	0.83
Pubertal status	8 prepubertal/10 pubertal	-	-	-

Data are expressed as median values. **Ht:** height**, Wt:** weight**, BMI:** body mass index, comparison with Z-score=0, * **p value**: p<0.05, comparison to Z-score=0

Table 2: Body composition analysis (bone mineral density of total body less head) in patients with Sotos syndrome.

Z-score BMD (TBLH)	N	Median	Minimum	Maximum	p-value
Unadjusted ("un")	12	0.68	-2.7	2.9	NS
Corrected for height-age ("Ht-A")	12	-0.55	-2.7	0.9	NS
Corrected for bone age ("BA")	12	-0.1	-2.3	2.9	NS
% difference ("Ht-A") from ("un")	12	-0.87	-13	0	NS
% difference ("BA") from ("un")	12	-0.54	-13	4.66	NS

Data are expressed as median values. **BMD**: bone mineral density, **TBLH**: total body less head, **"un"**: unadjusted, **"Ht-A"**: height for age, **"BA"**: bone age, * **p value:** p<0.05, comparison to Z-score=0, **NS**: non-significant

Table 3: Body composition analysis (bone mineral density of lumbar spine) in patients with Sotos syndrome.

Z-score BMD (LS)	N	Median	Minimum	Maximum	p-value
Unadjusted ("un")	15	-0.2	-2.7	3	NS
Corrected for height-age ("Ht-A")	15	-0.8	-2.8	0.9	NS
Corrected for bone Age ("BA")	15	-0.65	-2	2	NS
% difference ("Ht-A") from ("un")	15	0	-7.5	4	NS
% difference ("BA") from ("un")	15	0	-6.5	9.5	NS

Data are expressed as median values. **BMD**: bone mineral density, **LS**: lumbar spine, **"un"**: unadjusted, **"Ht-A"**: height for age, **"BA"**: bone age, ***p value:** p<0.05, comparison to Z-score=0, **NS**: non- significant

IU/d of cholecalciferol for three months. The median PTH was 33.5 pg/ml (Range: 17.2-81pg/ml) with normal values 12-62 pg/ml.

Bone turnover markers

Table 4 depicts the median Z-scores of bone formation markers (PICP, OC), and bone resorption markers (bTRAP5B, DPD/cr, UCa/Ucr). Two out of eighteen patients did not cooperate for blood sampling. Median Z-scores of all bone markers were within normal limits. IGF-1 levels were also normal, compared to the reference values of the kit used. Compared to Z-score=0, only PICP decrease reached statistical significance, implying affected bone formation.

Bone geometry and body composition

Bone geometry and body composition were derived by the TBLH scan, therefore data from twelve patients were analyzed (Table 5). Median value of bone strength was normal but in two out of twelve patients was low (< 2 SD in comparison to the general population).

Subgroup analysis

Between the following subgroups (patients with renal disorder vs patients without renal disorder) we found that median Z-score BMD LS ("BA") and Z-score BMD TBLH ("BA") were higher in the first group (Table 6). No significant differences were observed regarding bone turnover data and bone mineral

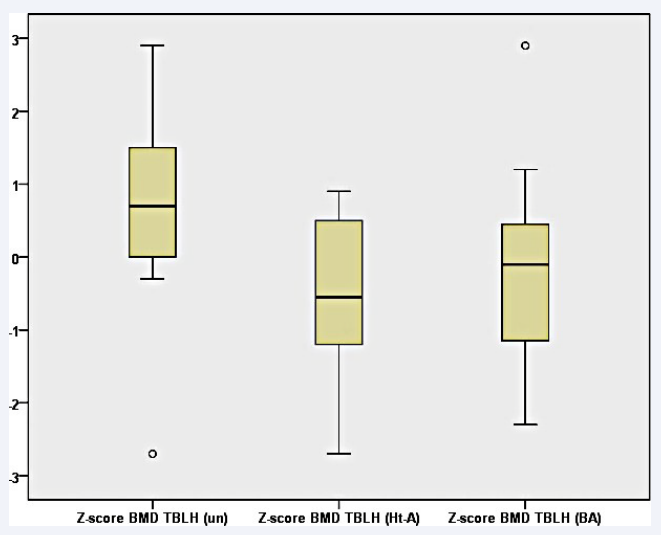

Figure A Boxplot: Bone mineral density (BMD) Z-scores of total body less head (TBLH): unadjusted (un), adjusted to height-age (Ht-A) and bone age (BA).

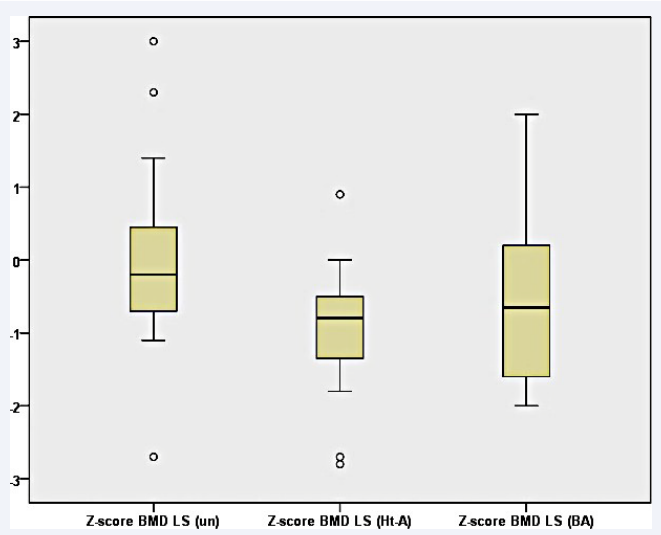

Figure B Boxplot-Bone mineral density (BMD) Z-scores of lumbar spine (LS): unadjusted (un), adjusted to height- age (Ht-A) and bone age (BA).

Table 4: Bone turnover data in patients with Sotos syndrome.

Variable	N	Median	Minimum	Maximum	p-value
PICP	16	-0.8	-2.4	0	0.01*
OC	16	-0.1	-2	1.4	0.95
DPD/cr	18	0.2	-3	6.7	0.58
UCa/UCr	18	0.23	0.11	0.64	0.42
bTRAP5B	16	0	-1.7	1.2	0.48

Data are expressed as median values. **BMD**: bone mineral density, **PICP**: procollagen type 1 C-terminal propeptide, **bTRAP5B**: bone tartate-resistant acid phosphatase type 5b urine deoxypyridinoline, **DPD**: urinary pyridinoline cross-links, **UCa**:urinary calcium exretion, **UCr**: urinary creatinine excretion, **OC**: osteocalcin, **IGF-1**:insulin-growth factor-1, *** p value:** p<0.05, comparison to Z-score=0

Table 5: Bone geometry - Body composition (bone fat) of patients with Sotos syndrome.

Variable in centiles (%)	N	Median	Minimum	Maximum
Bone size	12	97	23	99
Bone weight	12	32	1	90
Bone width	12	33	10	84
Muscle mass	12	50	9	96
Bone strength	12	31	1	97
Body fat	12	22	7	41.1

Table 6: Comparison of body composition parameters (BMD) between patients with renal disorder and patients without renal disorder.

Renal disorder	Z-score BMD ("BA")	N	Median	Minimum	Maximum	p-value
YES	LS	8	0.2	-0.2	2	0.01*
NO	LS	10	-1.45	-2	-0.6	0.01*
YES	TBLH	8	0.3	-0.1	2.9	0.03*
NO	TBLH	10	-1.15	-2.3	0.6	0.03*

Data are expressed as median values. **BMD**: bone mineral density, **LS**: lumbar spine, **TBLH:** total body less head, "**BA**": bone age, *** p value:** p<0.05, comparison to Z-score=0

Table 7: Correlations in patients with Sotos syndrome.

Variable	OC/ Z-score BMD LS ("BA")	(UCA/UCr)/ Z-score BMD TBLH ("BA")	Muscle mass / Z- score bTRAP5b
r (coefficient)	+0.575	- 0.771	- 0.731
p-value	0.03*	0.02*	0.04*

BMD: bone mineral density, **TBLH:** total body less head**, LS:** lumbar spine, **OC**: osteocalcin, **UCa**: urinary calcium excretion, **UCr:** urinary creatinine excretion, **bTRAP5b**: bone tartrate-resistant acid phosphatase type 5b, *** p value:** p<0.05

density in the other subgroups: patients with vs without scoliosis, prepubertal vs pubertal patients.

Correlations

A positive correlation was found between Z-score BMD LS ("BA") and OC (Table 7, Figure. C). In addition, a negative correlation was found between Z-score BMD TBLH ("BA") and UCa/Ucr (Table 7, Figure D). Finally, a negative correlation was found between Z-score bTRAP5B and muscle mass (Table7, Figure E). Any other correlation between imaging and laboratory data did not reach statistical significance.

DISCUSSION

Current data about skeletal health in patients with overgrowth syndrome are limited and this is the case with Sotos syndrome as well. To our knowledge, there is a lack of information on bone health in this particular syndrome in current bibliography. This study provides data on the skeletal status of eighteen Sotos patients.

We observed that scoliosis was frequent and should be looked for. In addition, similar musculoskeletal abnormalities such as long arms and legs, flat feet (pes planovalgus) and genu valgum were observed in all patients, so routine orthopedic assessment is important. Exercise, if possible, should be part of the daily routine, due to its beneficial skeletal effects [12]. In children with scoliosis, physiotherapy scoliosis specific exercises (PSSE), individualized to each patient's spine curvature, could be of value, according to the 2011 International Society on Scoliosis Orthopedic and Rehabilitation Treatment (SOSORT) [20].

In our cohort, Sotos patients with a renal disorder had higher BMD values. Given that all patients had normal kidney function,

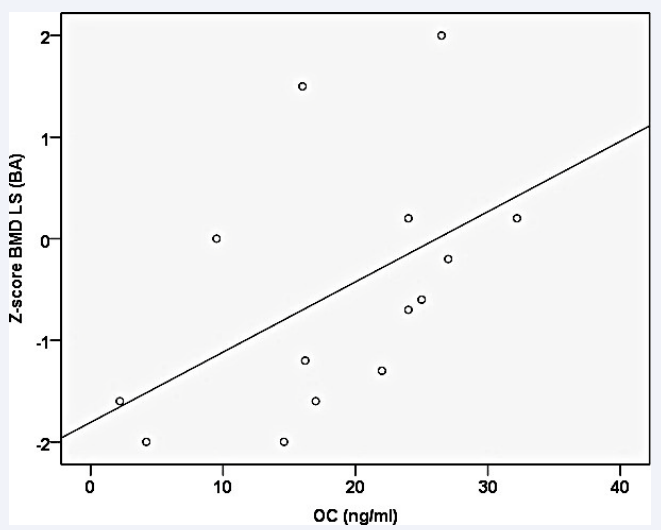

Figure C Linear correlation (trend) between bone mineral density Z-scores of lumbar spine (LS) adjusted to bone age (BA) and osteocalcin (OC).

In x-axis (fig.4), indicates 0. (eg: ,1 stands for 0.1)

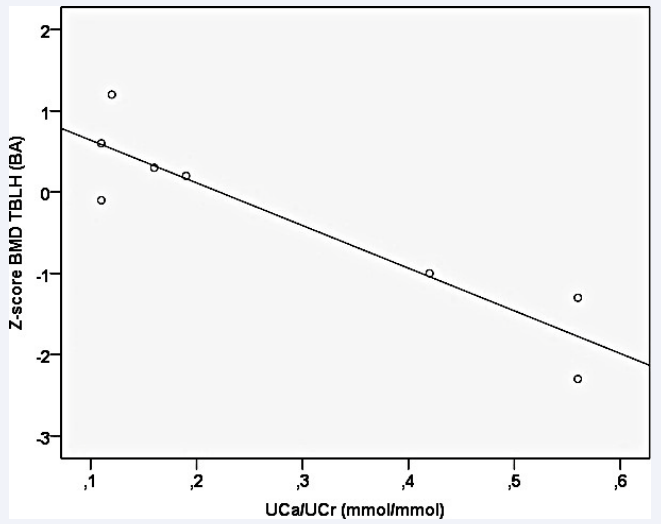

Figure D Linear correlation (trend) between bone mineral density Z-scores of total body less head (TBLH) adjusted to bone age (BA) and urine calcium excretion (UCA/UCr).

we can't draw any safe conclusion or provide an explanation, given the number of patients. Skeletal or other comorbidities did not affect the skeletal profile of our patient population in the rest of the subgroup analysis.

Calcium and vitamin D are two essential nutrients, long known for their role in bone health. An adequate level of vitamin D is required for an effective absorption of calcium which in turn is crucial for normal bone mineralization [21]. Calcium intake in our patients was estimated by a five-food item food frequency questionnaire (FFQ) and was compared to the recommended dietary allowances (RDAs), established by the Food and Nutrition Board (FNB) [19,22]. Notably, suboptimal Ca/24h intake was observed in all patients, so recommendations for adequate calcium intake through a balanced diet and/or calcium supplements should be given, where compliance is an issue. Greece is a sunny country and the study was performed in spring and summer, therefore most of the patients were vitamin D-sufficient. In case of vitamin D deficiency proper supplementation of cholecalciferol is indicated.

Unadjusted bone mineral density was overestimated in our patients, due to their tall stature and this could lead to false reassurance as to their bone mass assessment. Current literature focuses on the misdiagnosis of osteoporosis in patients with short stature, with less emphasis on tall stature; however, the same approach needs to be taken for tall patients as well, according to ISCD positions, to avoid misdiagnosis of "normal bone mineral density", when in fact it might be lower than expected [16,23]. This is an important message for everyday practice, not only for patients with Sotos syndrome, but also for other patients with tall stature, whose bone health may be compromised, i.e. patients with Marfan's or Klinefelter's syndrome [24,25]. Therefore, it is crucial that BMD values are adjusted for large bone size, in order to avoid false reassurance.

To explore whether bone age BMD adjustment is useful in this scenario, we also took a further step to evaluate bone age-adjusted measurements, in order to investigate possible correlations with laboratory parameters. It turns out that the bone-age adjusted BMD was even lower than height age- adjusted values. The difference between the two adjustment methods can be explained by the fact that bone age was relatively smaller than height-age in most of our patients. Nevertheless, regardless of the method of adjustment, the same conclusion was reached; the adjusted values were within normal limits (median Z-scores BMD between -2 and +2), thus there was no case of osteoporosis in our cohort, finding, which is reassuring and in accordance with the fact that no fractures were reported [16].

As far as bone geometry is concerned, median bone size was extreme for age (97th centile) and this was expected, because Sotos

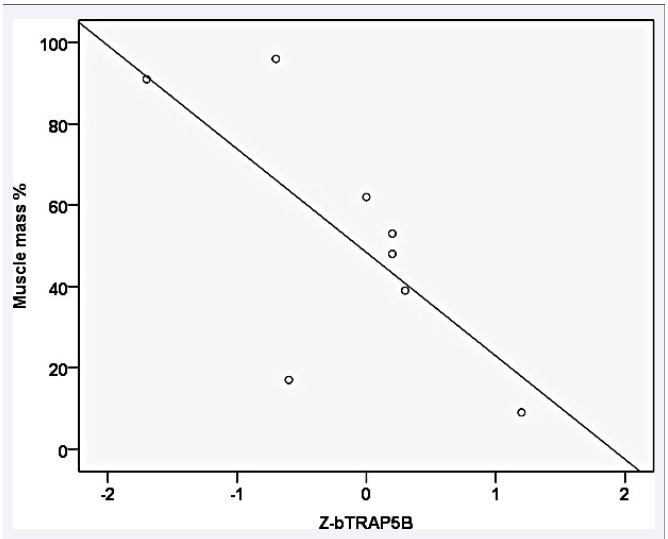

Figure E Linear correlation (trend) between muscle mass in percentile (%) and bone tartrate-resistant acid phosphatase type 5b (bTRAP5B) Z-score.

syndrome is an overgrowth disorder. The other bone geometry parameters (bone weight, bone width, and bone strength) did not deviate significantly from the 50th centile. No significant abnormalities were found in lean and fat mass assessment.

Bone markers were within normal values in our study, with the exception of PICP, a marker of bone formation, which deserves further consideration, as there is a gap in the literature on its role in overgrowth syndromes.

Interestingly, significant, meaningful correlations with laboratory indices were found only for Z-scores BMD corrected for bone age and not for height-age, so taking bone age adjustments into account might provide an insight in bone metabolism. Calcium excretion and bone age-adjusted total body BMD (proxy for cortical bone mass) are negatively correlated. Urinary calcium loss can exaggerate bone loss and this has been found in other disorders as well, e.g. idiopathic hypercalciuria [26]. Also, a significant positive correlation was found between bone-age adjusted LS BMD (proxy for trabecular bone mass) and osteocalcin, a marker for bone formation. It is possible that UCa/UCr and OC could therefore act as early markers of bone health in Sotos patients, before bone loss is apparent through bone densitometry.

Finally, a strong negative correlation was found between Z-score bTRAP5b and muscle mass. It is well known that there is cross-talk between muscle mass and bone. Mechanical loading promotes both muscle and bone acquisition, thus affecting bone geometry [27]. A possible explanation is that an increase of bTRAP5b, which is a marker of bone resorption and signifies bone loss, could theoretically lead to a further loss of muscle mass. The interaction between muscles and bone are truly complex. The role of myokines and osteokines and their effect on bone tissue and muscle respectively have been described [28]. Current data about bTRAP5b and muscle mass in particular are lacking; however, there is vivid interest in the muscle-bone interaction and our finding deserves further investigation [29].

Strengths and limitations of the study

Our study had strengths and limitations. Among the strong aspects is the fact that a holistic and systematic approach of skeletal assessment was performed in patients with Sotos syndrome for the first time, i.e. clinical examination, bone mineral density measurement and bone profile (bone markers, bone geometry, body composition) assessment were all part of our study.

The main limitation was the small number of patients included in our study. However, considering the rarity of the syndrome and the equally small number of young population aged five to eighteen years in Greece (latest recorded population number: 1.597.625), the number of participants could not have been larger [30]. Finally, the use of a control group was not approved.

CONCLUSION

Based on the thorough skeletal assessment in our cohort with Sotos syndrome, which combined clinical, imaging and laboratory data, there was no evidence of osteoporosis. From a methodological point of view, it seems that bone mineral density adjustment with bone age is valuable, as it reflects the bone profile of our patients more effectively than with height-age corrections and also correlates significantly with metabolic bone markers. Urinary calcium excretion and osteocalcin could potentially have a prognostic value for skeletal health in patients with Sotos syndrome and they might be used as a means of targeting the most suspicious cases. To ensure optimal bone health of Sotos patients during transition in adulthood, longer follow up is justified, as well as further research in bigger cohorts with this disorder, in an effort to expand the knowledge on this subject.

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