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ORIGINAL ARTICLE

Quantitative ultrasound of the hand phalanges in patients with genetic disorders: a pilot case-control study

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Abstract Skeletal status in subjects with genetic disorders rarely has been a matter of interest, and the risk for osteoporotic fracture in this population is not known. The aim of this study was to estimate ultrasound values in subjects with genetic disorders. In the study 50 patients (36 boys and 14 girls, mean age 11.8 ± 2.9 years) and 528 healthy controls matched for age and body size (380 boys and 148 girls, mean age 11.9 ± 2.5 years) were evaluated. Patients with the following disorders were included: Down syndrome, Martin-Bell syndrome, Marfan-Mass phenotype and others. Bone status was assessed by quantitative ultrasound (QUS) of hand phalanges using DBM Sonic 1200 (IGEA, Carpi, Italy), which measures amplitude-dependent speed of sound (Ad-SoS, m/s). Ad-SoS was significantly lower in patients than in controls (in the whole group $1{,}915 \pm 69$ m/s vs. $1{,}970 \pm 62.0$ m/s, $P < 0.0000001$; in males $1{,}917 \pm 73$ m/s vs. $1{,}972 \pm 63$ m/s, $P < 0.000001$; in females $1{,}910 \pm 58$ m/s vs. $1{,}963 \pm 58$ m/s, $P < 0.01$). Ad-SoS correlated significantly with age and body size (except for Ad-SoS with age in female patients). In all subgroups of patients (except for the subjects with Marfan-Mass syndrome) Ad-SoS values were significantly lower than in controls. In a multiple, stepwise regression analysis of Ad-SoS on age and body size, in the whole group of patients age and height had significant influence on Ad-SoS, and in controls age, height and weight. In conclusion, the study shows significantly lower phalangeal ultrasound values in subjects with different genetic disorders compared to normal healthy persons.

Keywords Genetic disorders · Hand phalanges · Quantitative ultrasound

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Introduction

Bone status in persons with genetic disorders only rarely has been a matter of interest in studies published in the medical literature, with the exception of osteogenesis imperfecta. Several reasons such as hypogonadism, low level of physical activity, small body size, some medications or skeletal abnormalities resulting from the disease per se may contribute to skeletal health in subjects with genetic disorders [1, 2]. Some previously published studies suggest that this group of persons may be at higher risk of fracture than the general community [1, 2, 3]. Measurement of bone mineral density (BMD) at the spine or hip by dual energy X-ray absorptiometry (DXA) is the most popular technique for bone status evaluation. Because accurate positioning is required, these measurements are difficult to perform in populations such as the group we studied. DXA is also connected with a low dose of ionizing radiation, which is an important factor in the evaluation of children. BMD measurements are also dependent on the size of the measured bones, which are important in measurements performed in children and adolescents. Recently, quantitative ultrasound (QUS) of hand phalanges as a method of bone status evaluation was developed. This method is free of ionizing radiation, and the device is portable. In several studies measurements of hand phalanges allowed the detection of bone changes resulting from growth [4, 5], some medications [6, 7], aging or postmenopause [8, 9]. In cross-sectional studies [6, 10,

11, 12, 13] this method proved to be able to discriminate between healthy individuals and those with different types of low-trauma fractures. In one longitudinal study, phalangeal ultrasound measurements were able to predict hip fracture in females [14].

The aim of this study was to compare ultrasound values between children and adolescent subjects with genetic disorders and age-matched controls. The assessment of skeletal status in such a population ought to provide important data about the presence and the degree of skeletal abnormalities in subjects with genetic disorders. Because of several factors mentioned earlier occurring in subjects with genetic disorders, bone status in this population may differ from bone status in a normal, healthy population.

Subjects and methods

Subjects

The group studied was recruited from patients of the Outpatient Genetic Clinic. A total of 85 parents of persons with genetic disorders were invited by mail to participate in the study, and 50 persons answered our invitation and came for bone measurements. The following genetic disorders were noted: chromosomal aberrations (9 persons with Down syndrome), single-gene human defects (15 subjects with Martin-Bell syndrome, 8 with Marfan-Mass phenotype) and 18 subjects with other disorders (1 neurofibromatosis syndrome type I, 2 Russel-Silver syndromes, 1 microcephaly-AR, 1 Rett syndrome, 3 hypohidrotic ectodermal dysplasia syndromes, 2 Seatleis syndromes and 8 nonspecific mental retardations of unknown etiology, probably X-linked). Down syndrome is caused by trisomia of chromosome 21. Physical and mental development are retarded. Microcephaly, a flattened occiput and short stature are characteristic.

In subjects with Martin-Bell syndrome fragile X-sites in the long arm of chromosome X occurs. This dynamic disorder is a very subtle dysmorphic syndrome and can be difficult to diagnose clinically. Persons with this disorder are mentally retarded and physically overactive, but they have poor musculoskeletal coordination, a tendency to obesity and also show hyperextensibility of the joints and hyperreflection of the lower limbs.

The Marfan-Mass syndrome is a disease of systemic connective tissue disorders. Mental development is not affected. The main symptoms of this syndrome in the skeletal system include: pectus carinatum, reduced upper to lower segment ratio or span to height ratio greater than 1.05, joint hypermobility and tall stature. Other genetic disorders are characterized by mental retardation, short stature and poor musculoskeletal coordination.

The diagnosis of Down syndrome was established on cytogenetic study; in persons with Martin-Bell syndrome the diagnosis was confirmed by molecular study, and other patients were classified using clinical signs and specific dysmorphic features. Parents agreed to ultrasound evaluation of their children.

Five hundred twenty-eight healthy persons (380 boys and 148 girls) who underwent ultrasound measurements made up the control group. All these subjects were pupils randomly selected from schools in the same industrial urban region. The control group was selected from a whole group of 1,020 children to obtain age-matched subjects. Also weight, height and body mass index (BMI) did not differ significantly among all patients and all controls, and among patients and controls in both genders. In controls no additional reasons affecting bone status (diseases or medications) were noted. Also patients were not treated with drugs with potential influence on bone metabolism and prolonged diseases (liver, kidney, thyroid gland), and stomach or intestinal surgery did not take place in patients. Clinical characteristics of patients and controls are given in Table 1. The local ethics committee gave permission for the study.

Method

Skeletal status was assessed by ultrasound measurements of proximal phalanges using a DBM Sonic 1200 device (IGEA, Carpi, Italy), which measures amplitude-dependent speed of sound (Ad-SoS, m/s) in the distal metaphyses of the proximal phalanges of the second through fifth fingers of the nondominant hand. This unit consists of two probes mounted on an electronic caliper, one emitter and one receiver. The latter records the ultrasound energy after it has crossed the phalanx. Ad-SoS in bone tissue is calculated considering the first signal with an amplitude of at least 2 mV at the receiving probe; thus, the measured speed of sound is amplitude dependent. Acoustic coupling was achieved using a standard ultrasound gel. All measurements were carried out by the same operator. In vivo precision was assessed by RMS_CV calculated accordingly to the proposition by Gluer et al. [15]. Seventy measurements were made in 14 healthy persons (measured five times each) by the same operator (W.P.). RMS_CV was 0.38%.

Statistical analysis

Calculations of means and standard deviations and linear regression analyses were performed using the Statistica program run on an IBM computer. Statistical analyses were performed in all patients and separately for the subgroups with Down syndrome, Martin-Bell syndrome, Marfan-Mass syndrome and other subjects. Z-scores (SD decrease from age- and sex-matched normal value) were automatically calculated by a software device using data provided by the manufacturer. Relationships between Ad-SoS and body size and age were performed using a simple linear regression analysis. The pattern of age-related changes in Ad-SoS was applied

Table 1 Clinical characteristics of patients and controls

	All patients, $n=50$	All controls, $n=528$	Male patients, $n=36$	Male controls, $n=380$	Female patients, $n=14$	Female controls, $n=148$
Age (years)	11.8 ± 2.9 8–18	11.9 ± 2.5 8.6–18	12.3 ± 3.0 8–18	12.2 ± 2.5 8.6–18	10.6 ± 2.3 8.2–16.6	10.7 ± 2.1 8.7–17.5
Height (m)	1.47 ± 0.2 1.02–1.97	1.49 ± 0.2 1.2–1.9	1.5 ± 0.21 1.15–1.97	1.52 ± 0.16 1.22–1.9	1.4 ± 0.19 1.02–1.71	1.41 ± 0.13 1.2–1.8
Weight (kg)	41.8 ± 19.7 17–107	41.8 ± 14.4 18–102	44.7 ± 21.5 20–107	44.4 ± 14.8 21–102	34.4 ± 12.1 17–60	35.2 ± 10.8 18–72
BMI (kg/cm^2)	18.2 ± 4.6 10.7–31.6	18.2 ± 3.0 12.6–31.7	18.6 ± 4.7 11.5–31.6	18.6 ± 3.1 13.0–31.7	17.3 ± 4.4 10.7–26.6	17.2 ± 2.51 12.6–25.9

Values are expressed as mean +/− SD and range

Table 2 Ultrasound values in patients and controls

	All patients, $n=50$	All controls, $n=528$	Male patients, $n=36$	Male controls, $n=380$	Female patients, $n=14$	Female controls, $n=148$
Ad-SoS (m/s)	*1,915 ± 69	1,970 ± 62	**1,917 ± 73	1,972 ± 63	***1,910 ± 58	1,963 ± 58
Z-score	*−1.34 ± 1.3	−0.06 ± 1.05	**−1.36 ± 1.31	−0.05 ± 1.08	***−1.29 ± 1.31	−0.071 ± 0.96

*Value significantly lower versus all controls with $P<0.0000001$, **value significantly lower versus male controls with $P<0.000001$, ***value significantly lower versus female controls with $P<0.01$

Table 3 Ultrasound values in subgroups of patients

	Patients with Down syndrome, $n=9$	Patients with Martin-Bell syndrome, $n=15$	Patients with Marfan-Mass syndrome, $n=8$	Other patients, $n=18$
Ad-SoS (m/s)	*1,888 ± 55	**1,914 ± 62	n.s. 1,997 ± 69	**1,894 ± 56
Z-score	**−1.24 ± 0.91	**−1.47 ± 1.02	n.s. 0.01 ± 1.09	**−1.84 ± 1.34

n.s. Value not significantly different versus control group, *value significantly lower versus control group with $P<0.00001$, **value significantly lower versus control group with $P<0.001$

by different curve-fitting functions (linear, quadratic or cubic models). Stepwise, multiple regression analyses were carried out to evaluate the impact of body size and age on Ad-SoS values. Because of the relatively small number of patients, multiple regression was carried out for the whole group of patients and all controls. Differences between mean values for body size, Ad-SoS and Z-scores were established using the Student's *t*-test. Distribution of body size, Ads-SoS and Z-scores was normal as confirmed by the Smirnoff-Kologomogorov test.

Results

Ad-SoS values and Z-score values in all patients, all controls and for both genders are given in Table 2. Mean values of Ad-SoS and Z-scores were significantly lower in patients than in healthy subjects in the whole group (1,915 ± 69 m/s vs. 1,970 ± 62 m/s, $P<0.0000001$) and also in both genders (in males 1,917 ± 75 m/s vs. 1,972 ± 63 m/s, $P<0.000001$; in females 1,910 ± 58 m/s vs. 1,963 ± 60 m/s, $P<0.01$). Ad-SoS values and Z-scores were also significantly lower in the subgroups of patients compared to controls except for the Marfan-Mass subgroup, in which Ad-SoS was nonsignificantly higher than in controls. These values are presented in Table 3. Because of the lower mean age of subjects with Down syndrome than the mean age of the whole control group, a new age-matched control group consisting of 407 subjects was created from all controls (mean age 10.8 ± 1.5 years). The mean value in Ad-SoS and Z-score in patients with Down syndrome was significantly lower in comparison to Ad-SoS in controls (Ad-SoS 1,947 ± 37 m/s, Z-score −0.06 ± 0.95). Figure 1 presents Ad-SoS values for subgroups of patients and controls. In the figure, the best fit of Ad-SoS with age was expressed by a polynomial function separately for all patients, and all patients are shown. In a simple linear regression analysis of Ad-SoS with age and body size, several significant equations were obtained, and they are presented in Table 4 (only coefficient of correlation between age and Ad-SoS in female patients was not significant). The lack of significant relationship in female patients is probably due to the small number of subjects in this group. Multiple, stepwise regression analyses of Ad-SoS with age and body size were performed in groups of all patients and all controls, and the following relationships were obtained: in patients Ad-SoS = 1,557 m/s + 2.4× height (m), ($r=0.73$, SEE = 49.0, $P<0.00001$) and in controls Ad-SoS = 1,608 m/s + 9.9 × age (years) + 1.9× height (m) −1.0× weight (kg) ($r=0.66$, SEE = 46.5, $P<0.00001$).

Discussion

Little is known about bone status among subjects with genetic disorders assessed by QUS. In Aspray et al.'s [1] study QUS as a method of evaluating bone status in such a population was used. In that study a large sample of persons described as mentally retarded were evaluated. The authors have found that ultrasound values at the calcaneus were significantly lower in both genders in comparison to healthy, control individuals. We reported similar results, but it is difficult to compare directly these two studies, because in Aspray et al.'s study [1] no detailed description of the material studied is given. Also, skeletal sites measured are different, but—despite that—calcaneus (weight-bearing and almost purely trabecular bone) and hand phalanges (non-weight-bearing and mostly cortical bone) revealed similar trends of changes.

In our study subjects with genetic disorders and controls were matched for age. Body size did not differ significantly between patients and controls, so significantly lower values of Ad-SoS in patients cannot be attributed to potential differences in age or anthropometric parameters. Of course, in the study we were not able to reveal other factors potentially influencing skeletal status. We can only hypothesize that some mechanisms (hypogonadism, low physical activity,

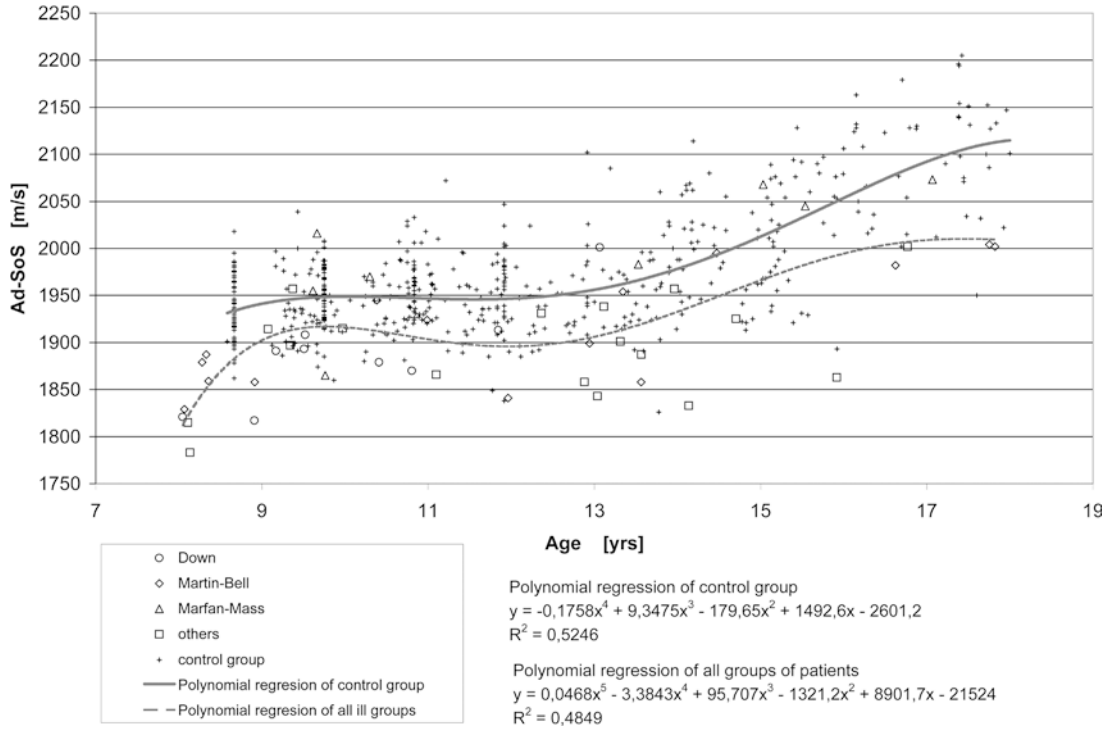

Fig. 1 Ad-SoS values in subgroups of patients and in controls

inadequate sun exposure, skeletal abnormalities) are involved in the pathogenesis of changes in skeletal status in subjects with genetic disorders. In the studied group, patients with several genetic abnormalities were evaluated, and it was not possible to divide patients according to the presence or absence of common severe features of genetic disorder. In our study skeletal status was assessed in the whole group of patients and separately for each type of disorder. Such analysis of the results provides clinically more precise data. In other studies [2, 16, 17], the subjects with Down syndrome had significantly lower BMD than healthy age-matched controls, and our results are similar. We did not find any data on BMD or QUS measurements in other genetic disorders than Down syndrome, and direct comparisons are not possible. Our data indicate that bone status in subjects with genetic disorders needs to be more extensively evaluated. It is an important clinical meaning of the study. Serious abnormalities revealed in our trial ought to be followed by future studies with parallel use of different methods estimating various aspects of bone status and metabolism. Common use of peripheral DXA (central measurements are difficult to perform due to problems with adequate positioning), QUS and bone markers probably may give more information about the nature of skeletal disorders in subjects with different types of genetic disorders.

We also evaluated our subgroups separately, and they had significantly lower ultrasound values compared to healthy controls except for the subgroup with Marfan-Mass syndrome. The difference in Z-score values between patients and controls ranging from −1.84 for patients with other genetic disorder to −1.24 for patients with Down syndrome clearly shows the degree of abnormality in skeletal status. We have not yet found any published study on skeletal status in Marfan-Mass syndrome, and it is difficult to discuss our results. We can only suspect that skeletal status in regard to bone

Table 4 Correlations and regressions of Ad-SoS with age and body size

Regression equations	*r*	*P*
All patients		
Ad-SoS = 1,746.6 (m/s) + 14.2× age (years)	0.59	< 0.00001
Ad-SoS = 1,827.8 (m/s) + 2.1× weight (kg)	0.58	< 0.0001
Ad-SoS = 1,565.9 (m/s) + 2.4× height (cm)	0.7	< 0.000001
All controls		
Ad-SoS = 1,780.8 (m/s) + 15.8× age (years)	0.64	< 0.000001
Ad-SoS = 1,870.5 (m/s) + 2.37× weight (kg)	0.55	< 0.000001
Ad-SoS = 1,595.1 (m/s) + 2.6× height (cm)	0.64	< 0.000001
Male patients		
Ad-SoS = 1,720.5 (m/s) + 15.9× age (years)	0.64	< 0.0001
Ad-SoS = 1,824.4 (m/s) + 2.1× weight (kg)	0.59	< 0.001
Ad-SoS = 1,544.6 (m/s) + 2.5× height (cm)	0.7	< 0.00001
Male controls		
Ad-SoS = 1,772.5 (m/s) + 16.1× age (years)	0.64	< 0.000001
Ad-SoS = 1,869.8 (m/s) + 2.3× weight (kg)	0.54	< 0.000001
Ad-SoS = 1,574.5 (m/s) + 2.6× height (cm)	0.65	< 0.000001
Female patients		
Ad-SoS = 1,798.2 (m/s) + 10.5× age (years)	0.42	NS
Ad-SoS = 1,802.5 (m/s) + 3.1× weight (kg)	0.63	< 0.05
Ad-SoS = 1,566.5 (m/s) + 2.5× height (cm)	0.76	< 0.01
Female controls		
Ad-SoS = 1,755.4 (m/s) + 19.3× age (years)	0.71	< 0.000001
Ad-SoS = 1,843.9 (m/s) + 3.4× weight (kg)	0.63	< 0.000001
Ad-SoS = 1,545.6 (m/s) + 2.9× height (cm)	0.65	< 0.000001

status in subjects with this disorder is not affected, or QUS is not able to reveal such abnormalities.

In the current study we also assessed the relationships of Ad-SoS with age and body size using simple linear and multiple, stepwise linear analyses. Correlation of Ad-SoS with age ($r = 0.59$) was very close to the value obtained in our previous study [4] performed in a population of healthy children ($r = 0.58$). A weaker, nonsignificant relationship with age occurred in female patients ($r = 0.42$). A correlation of Ad-SoS with age in female controls was much stronger ($r = 0.71$). Figure 1 provides an interesting view concerning age-related changes in Ad-SoS. To the age of 15 years, the curve for patients and controls showed similar trends, though the curve for patients was shifted below. After the age of 15 years, no further increase with age in Ad-SoS in patients was observed, while in controls Ad-SoS increased permanently. Because the upper age was limited to 18 years, we can only suspect that peak values of Ad-SoS in patients will be significantly lower than in the normal population. Correlations with weight and height in the current study were slightly stronger than those obtained in the previously published study [4]. In patients, r values were 0.59 for weight in male patients and 0.63 in female patients, and in the earlier study [4] the r value was 0.43 in the whole population. The same comparisons for height showed the following coefficients of correlation: 0.70, 0.76 and 0.56, respectively. Multiple, stepwise linear regressions showed that in all patients only age and height significantly affect Ad-SoS values, while in controls, Ad-SoS was influenced by age, height and weight. The regression equation in controls is similar to that obtained previously in a normal population of Polish children [4].

Recently, an interesting study by Baroncelli et al. [5] performed in healthy young subjects aged 3–21 years was published. The authors used the same device, and at the age of 12 years Ad-SoS was about 1,950 m/s in males and about 2,000 m/s in females. These values are in the range of Ad-SoS values in our controls. However, the Italian investigators noted stronger correlations with age (r value 0.87 in both genders), weight ($r = 0.77$ in males and 0.82 in females) and height ($r = 0.81$ in males and 0.84 in females).

The current study has several limitations: the relatively small group of patients studied, especially females, and lack of longitudinal measurements. Also, a weakness of the study is that common analysis of a group consisted of different genetic disorders, which did not allow for assessment of the role of severity of genetic disorders. We did not collect data on pubertal status or bone age, and these factors were not evaluated in the study. However, the majority of patients studied had not yet experienced the onset of sexual maturation. Another weakness of our trial is the lack of data concerning the Ultrasound Bone Profile Index (UBPI), but the software of our older device does not calculate this parameter. It also will be interesting to compare ultrasound results with data on bone mass, but adequate positioning necessary for spine or total body measurements were difficult to perform in subjects with genetic disorders. A peripheral DXA machine, which would have been more appropriate for our group, was not available.

The current results ought to be treated as a preliminary report only. Subjects with genetic disorders showed lower ultrasound values than normal subjects. This observation is the most important information derived from the study and should be followed by some preventive procedures concerning diet or physical activity. Also, further studies aimed at the identification of factors influencing skeletal status in individuals with genetic disorders are necessary. General trends of changes in ultrasound parameters similar to observations obtained for BMD suggest that both DXA and QUS are useful for evaluation of bone status in subjects with genetic disorders. However, some features of QUS, such as the lack of ionizing radiation, portability of devices and low costs, make this method more attractive than DXA. Also easy positioning, especially for such populations as subjects with genetic disorders or children, is a very important factor.

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