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ORIGINAL ARTICLE

Analysis of volumetric BMD in people with Down syndrome using DXA-based 3D modeling

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Abstract

Summary We analyzed volumetric bone mineral density, by 3D analysis, in 76 people with Down syndrome and 76 controls. People with Down syndrome, particularly men, have a lower hip volumetric bone mineral density than the general population. Besides, volumetric bone mineral density declines more rapidly in Down syndrome.

Introduction People with Down syndrome (DS) have a lower areal bone mineral density (aBMD) estimated by dual-energy X-ray absorptiometry (DXA). However, they have smaller-sized bones, which could influence the measurements. Therefore, our objective was to determine volumetric BMD in these patients.

Materials and methods We included 76 outpatients with DS and 76 control healthy volunteers matched for age and sex distribution. Clinical data were obtained with a standardized interview and physical exam, including age, sex, height, weight, and body mass index (BMI). aBMD was measured by dual-energy X-ray at the femoral neck (FN) and total hip (TH). The 3D-SHAPER® software (version 2.8, Galgo Medical, Barcelona, Spain) was used to derive 3D analysis from participants' hip DXA scans.

Results DS femurs had a similar 3D geometry, compared with the femurs of controls. However, 3D analysis showed that participants with DS had smaller cortical thickness (1.84 mm ± 0.17 vs. 2.02 ± 0.20 mm; $p < 0.0001$), cortical vBMD (777 ± 49 mg/cm^3 vs. 809 ± 43 mg/cm^3; $p < 0.0001$), and cortical sBMD (143 ± 19 mg/cm^2 vs. 164 ± 22 mg/cm^2; $p < 0.0001$). After adjustment for age and BMI, all 3D measurements remained lower in DS than in controls. These differences were more marked in men than in women. vBMD decreased with age in controls and DS, but the decline was greater in DS for all 3D parameters.

Conclusion People with DS, particularly men, have a lower hip vBMD than the general population. Besides, vBMD declines more rapidly in DS.

Keywords Volumetric · Bone mineral density · 3D modeling · Osteoporosis · Down

Introduction

Down syndrome (DS) is the most frequent chromosomal disorder in live newborns and the first cause of congenital intellectual disability [1]. Several studies reported that people with DS have a lower areal bone mineral density (aBMD) [2–5]. However, skeletal size differences can be responsible for the apparent differences in aBMD, estimated by dual-energy X-ray absorptiometry (DXA), between people with DS and general population [6]. Few studies have analyzed volumetric bone mineral density (vBMD) in DS, the majority of them using quantitative computed tomography (QCT) or published formulas [7]. Recently, 3-dimensional (3D)-DXA modeling methods were proposed to overcome the limitations of DXA. 3D measurements obtained by DXA were validated against QCT [8, 9]. QCT has demonstrated to be valuable to predict fracture risk [10–14].

The aim of the present study was to evaluate vBMD and bone geometry at the proximal femur in people with DS using DXA-based 3D modeling methods, and to compare DS patients with healthy controls to deepen our knowledge of the bone mass status in DS.

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Materials and methods

Study population

We included 152 individuals (76 with DS and 76 controls; 50% male) over 18 years of age. Patients with DS were recruited from our DS clinic at the University Hospital Marqués de Valdecilla and the Down Syndrome Foundation of Cantabria (Spain). A convenience control group was recruited among volunteers matched for age and sex distribution. All participants were studied in the same period (November–December 2015). Their standard DXA measurements have been previously published [6]. Exclusion criteria were the refusal to participate in the study, pregnancy, previous osteoporosis treatment, or physical disability that did not allow the realization of the densitometry. Data were obtained with a standardized interview and physical exam, including age, sex, height (cm), weight (kg), and body mass index (BMI; kg/m^2). The study protocol was approved by the Institutional Review Board and all patients gave written informed consent.

DXA measurements

At baseline, BMC (bone mineral content in g), area (cm^2), and aBMD (g/cm^2) were measured by DXA (Hologic QDR 4500, Waltham, MA) at the femoral neck (FN) and total hip (TH) regions. In vivo precision was 0.47% in FN and 0.42% in TH.

DXA-based 3D modeling

The 3D-SHAPER® software (version 2.8, Galgo Medical, Barcelona, Spain) was used to derive 3D analysis from participants' hip DXA scans. Briefly, the method uses a 3D statistical shape and density model that is registered onto the DXA scan to obtain a patient-specific 3D model of the proximal femur (femoral shape and 3D bone density image) [8]. The cortex is segmented on the 3D image by fitting a function of the cortical thickness and density, the location of the cortex, the density of surrounding tissues, and the imaging blur to the density profile computed along the normal vector at each node of the proximal femur surface mesh [15]. The software outputs 3D measurements at the total femur region of interest, including the trabecular and integral (i.e., cortical plus trabecular) volumetric BMD (vBMD, in mg/cm^3), and the cortical surface BMD (cortical sBMD, in mg/cm^2, computed as the multiplication of the cortical vBMD in mg/cm^3 and the cortical thickness in cm). The accuracy and precision of 3D-SHAPER measurements were evaluated against QCT in previous works [10, 16].

Statistical analysis

Results were expressed as mean (SD) or percentages, as appropriate. Student's t test was used to analyze the differences between groups for continuous variables. The Mann Whitney U test was used when the variable did not follow a normal distribution. The chi-squared test or Fisher's exact test was used to identify differences in categorical variables. The analysis of variance (ANOVA) was used to adjust by age and BMI. A value of $p < 0.05$ was considered statistically significant. All analyses were performed using the SPSS software version 20 for Windows (IBM corp., Armonk, NY, USA).

Results

The mean age was 33 ± 10 years, both in DS and controls. DS individuals had lower height (151 ± 6 cm vs. 169 ± 8 cm; $p < 0.0001$) and lower weight (60.3 ± 11.0 kg vs. 69.2 ± 13.3 kg; $p < 0.0001$) than controls, but they have higher BMI (26.4 ± 4.4 kg/m^2 vs. 24.0 ± 3.4 kg/m^2; $p < 0.0001$). The values of BMC (g), area (cm^2), and aBMD (g/cm^2) hip (FN and TH) were lower in DS than in controls (Table 1). The patients with DS had more comorbidities than the control group. We found higher prevalence of treated hypothyroidism (37 in DS vs. 0% in controls; $p < 0.001$), congenital heart disease (21 vs. 7%; $p = 0.009$), epilepsy (7 vs. 0%; $p = 0.028$), cataracts (12 vs. 1%; $p = 0.008$), and skin disorders (12 vs. 0%; $p = 0.001$). Those results are in agreement with those previously published [6].

Figure 1 shows that, although smaller in size, DS femurs had a similar 3D geometry, compared with the femurs of controls. In particular, both groups showed similar geometry at the femoral neck. The 3D analysis showed that participants with DS had lower cortical thickness (1.84 mm ± 0.17 vs. 2.02 ± 0.20 mm; $p < 0.001$), cortical vBMD (777 ± 49 mg/cm^3 vs. 809 ± 43 mg/cm^3; $p < 0.0001$), and cortical sBMD (143 ± 19 mg/cm^2 vs. 164 ± 22 mg/cm^2; $p < 0.0001$). The differences in integral and trabecular vBMD were not significant (Table 1). The anatomical distribution of the differences at the cortex between DS and controls is shown in Fig. 2.

After the adjustment for age and BMI, all 3D measurements were lower in DS than in controls (Table 2). The sex-stratified analysis showed that men with DS had lower values than controls in all 3D parameters, whereas women with DS only showed significant differences in the cortical parameters (Table 2).

vBMD decreased with age both in DS and controls, but the decline was greater in DS (p value of the interaction 0.003 for trabecular vBMD, 0.002 for integral vBMD, and 0.001 for cortical vBMD) (Fig. 3).

Table 1 DXA and 3D-DXA measurements in both groups

	Down syndrome $N = 76$	Controls $N = 76$	p
DXA measurements			
BMC FN (g)	3.41 (0.63)	4.38 (0.91)	< 0.0001
Area FN (cm^2)	4.53 (0.49)	5.20 (0.55)	< 0.0001
aBMD FN (g/cm^2)	0.756 (0.128)	0.838 (0.115)	< 0.0001
BMC TH (g)	25.15 (0.33)	34.24 (9.10)	< 0.0001
Area TH (cm^2)	30.35 (4.12)	35.74 (5.98)	< 0.0001
aBMD TH (g/cm^2)	0.826 (0.116)	0.947(0.127)	< 0.0001
3D-DXA measurements			
Trabecular vBMD (mg/cm^3)	203 (48)	216 (40)	0.088
Integral vBMD (mg/cm^3)	329 (63)	345 (51)	0.084
Cortical vBMD (mg/cm^3)	777 (49)	809 (43)	< 0.0001
Cortical sBMD (mg/cm^2)	143 (19)	164 (22)	< 0.0001
Cth (mm)	1.84 (0.17)	2.02 (0.20)	< 0.0001

Mean (SD), *DXA* dual-energy X-ray absorptiometry, *aBMD* areal bone mineral density, *FN* femoral neck, *TH* total hip, *3D-DXA* three-dimensional dual-energy X-ray absorptiometry, *vBMD* volumetric bone mineral density, *Cortical sBMD* cortical surface BMD, *Cth* cortical thickness

Discussion

A lower aBMD in people with DS has been described. People with DS have several potential risk factors for low BMD, such as less physical activity, sarcopenia, poor calcium and vitamin D intakes, anti-epileptic medication use, frequent comorbidity, and lower peak bone mass [17–19]. However, few studies have analyzed vBMD, despite the important fact that the size of bone is lower in these people. The DS population has growth retardation and a limited growth span, resulting in a shorter height [20]. The cause is likely related to the excess copy of some genes located on chromosome 21, and a role of the dual-specificity tyrosine-(Y)-phosphorylation regulated kinase 1A (DYRK1A) gene has been suggested, but it has not been confirmed yet [21]. Whatever the mechanisms involved might be, patients with DS have smaller bones, which may influence areal BMD measurements. Some studies did not find differences between DS and controls after correcting for the bone size [22–24], but others reported that people with DS have lower vBMD [25, 26]. In people with DS, we previously published diverging results of areal and vBMD calculated by several mathematical formulas [6]. Now, we have analyzed vBMD in hip using a DXA-based 3D modeling technique and we can see that these people have lower values in all components analyzed (− 6.0% in trabecular vBMD, − 4.6% in integral vBMD, and − 8.9% in cortical vBMD) and also have smaller cortical thickness (− 8.9%) and cortical sBMD (− 3.9%) than general population. These results could be relevant and finally contribute to clarifying the controversy in this topic. In our study, the differences in parameters of vBMD between DS and controls are more pronounced in men. This population seems to be especially vulnerable to osteoporosis. The high prevalence of hypogonadism and hypoandrogenism in men with DS can contribute to explain those findings [20]. As previously reported, these men with DS had lower serum testosterone levels than controls (4.3 (1.6) ng/ml vs. 5.3 (2.0) ng/ml; $p = 0.02$) publication [6].

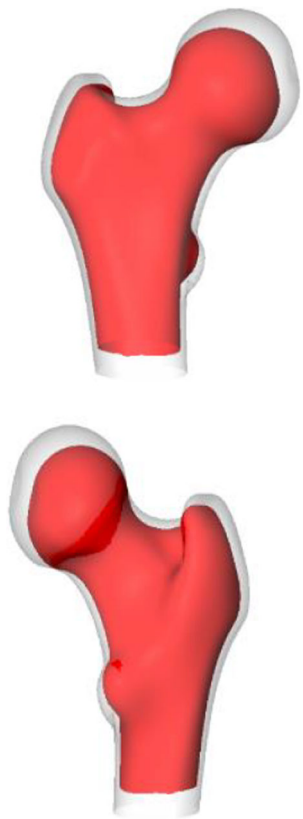

Fig. 1 Comparison between mean geometry of Down syndrome (red) and controls (gray)

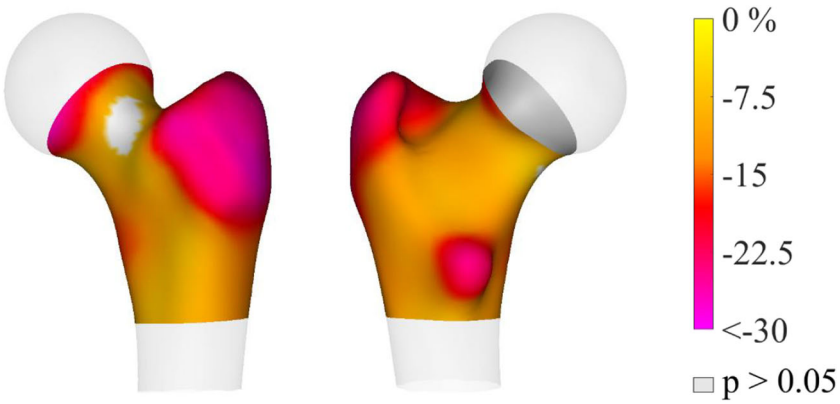

Fig. 2 Anatomical distribution of mean differences in cortical surface BMD between DS and controls. Non-significant differences are left in gray

Several studies suggested differences in hip morphology between DS and controls. The spectrum of skeletal anatomical abnormalities at hip included increased femoral anteversion and coxa valga, insufficient posterior acetabular coverage, and acetabular retroversion [27–29]. This was of particular importance, for differences in the morphology and geometry of the femur in people with DS could interfere with a correct measurement. However, we confirmed that the shape of the measurement area was similar in DS and controls, thus assuring the feasibility of the 3D analysis.

In this work, we also found that values of vBMD hip decreased with age in a more pronounced way in DS than in the

Table 2 3D measurements in both groups after adjustment for age and BMI

3D-DXA measurements	Down syndrome	Controls	*p*
All	*N* = 76	*N* = 76	
Trabecular vBMD (mg/cm^3)	199 (4)	220 (4)	0.001
Integral vBMD (mg/cm^3)	323 (5)	351 (5)	0.001
Cortical vBMD (mg/cm^3)	772 (5)	814 (5)	< 0.0001
Cortical sBMD (mg/cm^2)	141 (2)	166 (2)	< 0.0001
Cth (mm)	1.82 (0.02)	2.04 (0.02)	< 0.0001
Men	*N* = 38	*N* = 38	
Trabecular vBMD (mg/cm^3)	191 (5)	217 (5)	0.001
Integral vBMD (mg/cm^3)	311 (7)	342 (7)	0.004
Cortical vBMD (mg/cm^3)	774 (7)	816 (7)	0.0001
Cortical sBMD (mg/cm^2)	141 (3)	170 (3)	< 0.0001
Cth (mm)	1.81 (0.26)	2.08 (0.27)	< 0.0001
Women	*N* = 38	*N* = 38	
Trabecular vBMD (mg/cm^3)	208 (6)	222 (6)	0.19
Integral vBMD (mg/cm^3)	338 (9)	359 (8)	0.11
Cortical vBMD (mg/cm^3)	768 (7)	814 (7)	0.0002
Cortical sBMD (mg/cm^2)	142 (3)	162 (3)	0.00023
Cth (mm)	1.84 (0.00)	1.98 (0.03)	0.004

Mean (SD), *3D-DXA* three-dimensional dual-energy X-ray absorptiometry, *vBMD* volumetric bone mineral density, *Cth* cortical thickness, *p* adjustment for age (years) and BMI (body mass index kg/m^2)

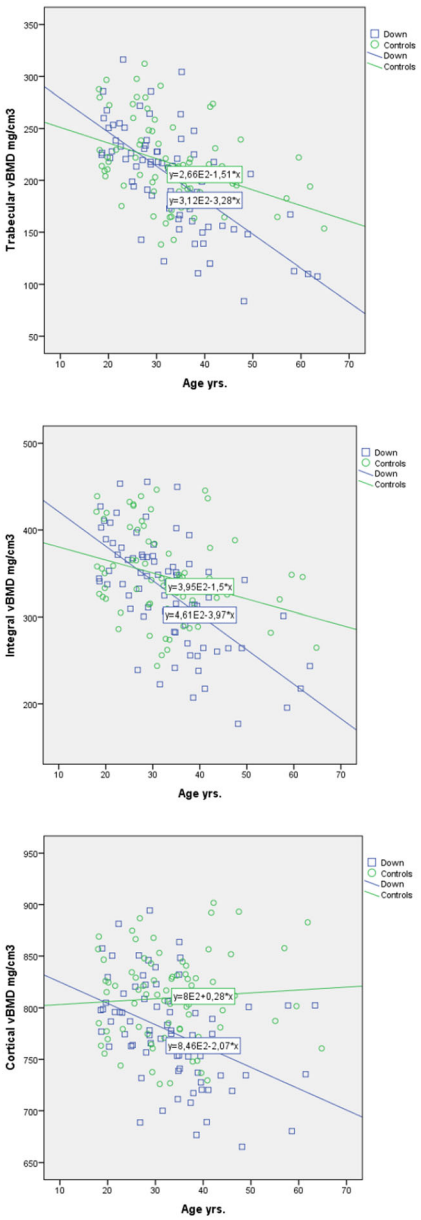

Fig. 3 Decline in vBMD with age

general population. Other authors showed similar results [18]. However, the prevalence of osteoporotic fractures in DS is controversial [30]. In our previous study, the prevalence of fractures was similar in DS and controls (11% vs. 12%; $p = 0.35$), and most of these occur in the long bones (9 vs. 14%; $p = 0.23$) [6].

This study has some limitations, such as the sample size and the cross-sectional design. Also, the validation of the accuracy and precision of the D modeling method used in this study did not include patients with DS. Although the 3D modeling process converged in all subject included in the current study, the accuracy and precision of 3D modeling methods in assessing DS patients should be investigated in future work. This study is the first analysis with DXA-3D in a cohort of adults with DS. We report a lower vBMD in hip especially in men with DS. The decline with age is more pronounced in these people.

Compliance with ethical standards

The study protocol was approved by the Institutional Review Board and all patients gave written informed consent.

Conflict of interest L. Humbert is stockholder and employee of Galgo Medical. Marta García Hoyos, José A. Riancho, and Carmen Valero declare that they have no conflicts of interest.

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