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Physical activity and bone mineral density at the femoral neck subregions in adolescents with Down syndrome

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Abstract

Background: Low bone mineral density (BMD) has been frequently described in subjects with Down syndrome (DS). Reduced physical activity (PA) levels may contribute to low BMD in this population. The objective of the study was to investigate whether PA levels were related to the femoral neck bone mass distribution in a sample of 14 males and 12 females with DS aged 12–18 years.
Methods: BMD was evaluated by dual energy X-ray absorptiometry (DXA) at the integral, superolateral and inferomedial femoral neck regions and PA levels were assessed by accelerometry. The BMDs between the sexes and PA groups (below and above the 50th percentile of the total PA) were compared using independent t-tests and analyses of covariance (ANCOVAs) controlling for age, height and body weight.
Results: No differences were found between the BMDs of males and females in any femoral neck region ($p > 0.05$). Females with higher PA levels demonstrated increased integral (0.774 g/cm^2 vs. 0.678 g/cm^2) and superolateral femoral neck BMDs (0.696 g/cm^2 vs. 0.595 g/cm^2) compared to those with lower PA levels ($p < 0.05$). In males, no differences ($p < 0.05$) were found in the BMDs between the PA groups.
Conclusions: This investigation shows that females accumulating more total PA presented increased BMDs at the integral and superolateral femoral neck regions (14.1% and 17.0%, respectively) when compared to their less active peers. These data highlight the importance of PA in females with DS to counteract their low bone mass and to improve their bone health.

Keywords: accelerometry; bone density; bone health; Down syndrome; femoral neck; physical activity.

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Introduction

Down syndrome (DS) is the commonest cause of intellectual disability with an estimated incidence between 1:750 and 1:1000 live births [1, 2]. Each year approximately 3000–5000 newborns present this chromosome disorder in the USA [3]. Among the features and developmental problems described in these persons [1], skeletal health has received a lot of attention in recent years [4–6]. Low bone mineral density (BMD) has been repeatedly reported [7–11] in DS subjects in comparison with their counterparts without DS. However, whether the low BMD found in DS subjects is due to their genetic condition or a consequence of their lifestyle is still unclear [7, 12].

Although the hip has been reported as a nonreliable site to be measured by dual energy X-ray absorptiometry (DXA) in growing children [13], it is the skeletal site with the highest clinical concern [14]. Furthermore, bone fracture rates are higher in people with intellectual disabilities

compared to those without intellectual disabilities (5.2 vs. 3 per 100 persons/year) [15, 16].

Hip fractures are determined by the material and structural properties of the proximal femur including bone mass distribution [17]. Bone mass distribution at the femoral neck may be visualized in a DXA scan by the location of the Ward's area – the area of minimum density in the femoral neck region. In the case of a good balance among the three trabecular bundles – the principal compressive, the secondary compressive and the tensile trabecular – the Ward's area is located at the middle of the neck width, suggesting an adequate bone mass distribution between the medial and lateral sides. A deterioration in the previously described groups of trabeculae forms the basis of the grading scheme proposed by Singh and colleagues [18]. These authors stratified the risk of femoral neck fracture in osteoporosis, the location being the Ward's area where the initial bone loss becomes significant. When the Ward's area is detected in the superolateral region of the femoral neck, a decline in the trabeculae of the secondary compressive group might be occurring. Therefore, the evaluation of several regions may inform about the possible imbalances in the femoral neck bone mass distribution.

The influence of physical activity (PA) on bone mass distribution at the proximal femur was analyzed recently in a longitudinal study with a 1-year follow-up in 10- to 12-year-old children [19]. It was found that mechanical loading induced by PA in girls and by lean mass in boys positively influenced the integral, superolateral and inferomedial femoral neck BMDs. In subjects with DS, reduced PA levels may contribute to low BMDs [6, 11]. It has been shown that adolescents with DS performing more PA, even without reaching the minimum established recommendations, have a lower risk of developing osteoporosis in future by having a higher BMD Z-score at the hip [12]. Furthermore, it has been shown that a low BMD and fracture incidence were associated in females but not in young male adults with intellectual disability [11]. Although an important and emergent approach, no research has investigated the effect of objectively measured PA on BMD at several regions of the femoral neck in subjects with DS.

The main purpose of this cross-sectional study was to investigate whether PA levels are related to the femoral neck bone mass distribution in a sample of males and females with DS aged 12–18 years. We hypothesized that the more physically active adolescents have better mineralization at the integral femoral neck, particularly at the superolateral femoral neck region, compared to their less active peers.

Materials and methods

This study is part of the biggest randomized controlled trial whose methods and procedures have been previously described [20].

The participants and their parents were informed about the protocol of this study, its benefits and risks. Written informed consent from the parents and verbal assent from the participants were obtained. The study design, protocol and consent forms were in accordance with the Helsinki Declaration of 1964 (revised in Fortaleza, 2013) and were reviewed and approved by the Research Ethics Committee of the Government of Aragón (CEICA, Spain) [C.I. PI10/026]. Then, the study was registered in a public database (ClinicalTrials.gov identifier [NCT02380638]). This work was done following the STROBE Guidelines reported elsewhere [21].

Participants

All the participants were recruited from different schools and institutions of Aragón (Spain). The inclusion criteria consisted of the following: age between 10 and 19 years, Caucasian with DS not taking medication affecting bone metabolism and able to exercise. The risk of cardiovascular events during physical effort was evaluated by a cardiologist. The participants were asked to continue with their habitual daily routines.

Initially, 34 participants with DS agreed to collaborate in this study. Then two participants declined to collaborate and another two did not meet the inclusion criteria described previously. After that, 30 participants were included in the study but two participants did not tolerate wearing the accelerometer for seven consecutive days and another two participants had blurred hip scans. Finally, 26 adolescents with DS (12 females) were analyzed in this cross-sectional study.

Anthropometric measures and puberty

The standing height of the participants (without shoes and with minimal clothing) was measured to the nearest 0.1 cm using a stadiometer (SECA 225, SECA, Hamburg, Germany). Their body weight was evaluated to the nearest 0.1 kg (SECA 861, SECA, Hamburg, Germany) following the procedures of the International Society for the Advancement in Kinanthropometry (ISAK) [22]. The body mass index (kg/m^2) was calculated according to the equation, body weight/height^2. Pubertal maturity was assessed by direct observation by a medical doctor according to the five stages proposed by Tanner and Whitehouse [23].

Bone assessments

BMD measurements of the nondominant leg were determined from a hip scan with DXA (pediatric version of the QDR-Explorer software, Hologic Corp. Software version 12.4, Bedford, MA, USA). The hip scans were performed according to the manufacturer's guidelines and the proximal femur regions were determined following the procedures defined in the QDR Reference Manual. All the participants were examined in the same position, with a specific cushion and

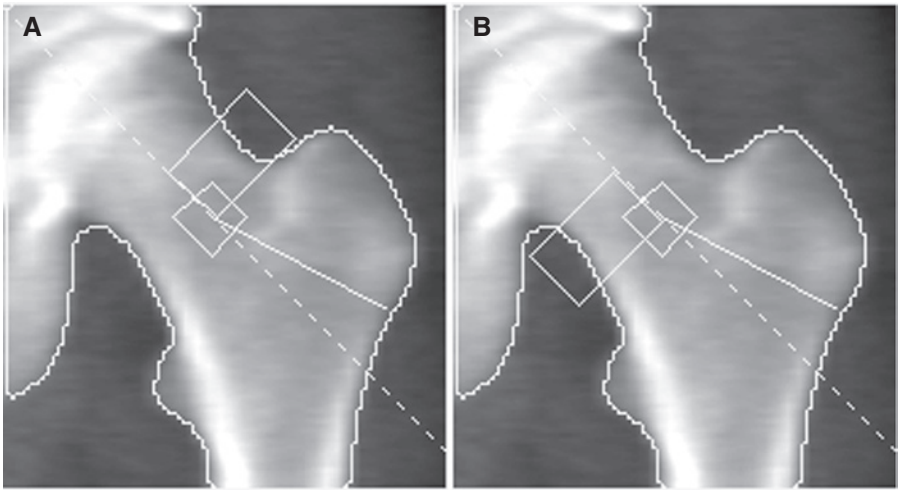

Figure 1: Manual analysis to determine BMD at the superolateral and the inferomedial femoral neck subregions.
Hip image from Hologic DXA scanner showing the superolateral (A) and the inferomedial (B) femoral neck subregions.

straps, provided by the DXA manufacturer for this scan specifically, so that the rotation of the hip was the same in every participant. The same technician conducted all femoral neck examinations, specifically the integral, superolateral and inferomedial BMD evaluations. To this end, we used the procedures described by Cardadeiro and colleagues [19]: for the superolateral BMD determination, the inferomedial neck box line was dragged toward the proximal femur axis up to reach the midline, drawing a box of 24×15 mm (Figure 1A). A symmetric procedure, using the superolateral box line, was carried out to determine the inferomedial region (Figure 1B). The DXA equipment was calibrated daily using a lumbar spine phantom following the manufacturer's guidelines. The in vivo coefficients of variation in measuring the bone mineral content and the BMD of our DXA were published previously [24].

Assessment of PA

The methodological considerations for measuring the PA are available in more detail elsewhere [12]. The PA was objectively assessed using the ActiTrainer uniaxial accelerometer (Actigraph, LLC, Pensacola, FL, USA), which has been previously validated [25], with 15-s epochs based on a previous study [26]. The participants were instructed to wear the accelerometer on the right hip for seven consecutive days [27]. Verbal instructions were given to the parents along with a time sheet to register when the device was placed on or removed. To be included in the analysis, the accelerometer had to provide at least 600 min/day and had to be worn for 4 days including at least a weekend day [28]. Water activities and sleeping were not registered. A 20-min period of continuous zero counts was automatically deleted during the data reduction with the R program [29] and considering the methodological concerns of Ojiambo and colleagues [30]. Time during sedentary behaviors and at different PA intensities (light, moderate or vigorous) was determined according to the cut-off points proposed by Evenson and colleagues [31] and recommended by Trost and colleagues [32], namely 25, 573 and 1002 counts/15-s epochs to separate sedentary behavior and light, moderate and vigorous PA, respectively. The total PA was calculated as the sum of minutes in light, moderate and vigorous activity; afterwards, the 50th percentile was used to divide the sample into high- and low-PA groups (HIGH and LOW).

Statistical analysis

Data were analyzed using the Statistical Package for the Social Sciences version 22.0 for Windows (SPSS Inc., Chicago, IL, USA), and significance was set at $p < 0.05$. The mean and standard deviation (SD) are given as descriptive statistics. Data distribution was analyzed using the Shapiro-Wilk normality test. Independent t-tests and the Mann-Whitney nonparametric test were performed to compare descriptive characteristics between males and females with DS when variables were or were not normally distributed, respectively. A χ^2-test was performed to evaluate the differences in the Tanner stage between the groups.

Independent t-tests and analyses of covariance (ANCOVAs) controlling for age, height and body weight were performed to compare the BMD variables between males and females with DS. These covariates were selected as the adolescents with DS were small for their age [33, 34]. The previous analyses were repeated to compare the BMD variables of the HIGH and LOW groups separately for males and females.

For the t-tests, the effect size was estimated considering the cut-offs defined by Cohen [35] – small: $d \leq 0.2$, medium: $0.2 > d < 0.8$ or large: $d \geq 0.8$. Since the effect sizes of small samples ($n < 20$) tend to be overestimated in ANCOVA using the previous approach, the correction factor suggested by Hedges [36] – small: $g \leq 0.4$, medium: $0.4 > g < 0.7$ or large: $g \geq 0.7$ was used [37].

Results

The physical characteristics of the participants are provided in Table 1. Females were smaller, with higher body

Table 1: Descriptive characteristics of participants with DS.

	Females (n = 12) mean ± SD	Males (n = 14) mean ± SD	Cohen's *d*
Physical characteristics			
Age, years	15.7 ± 2.9	16.5 ± 2.6	0.27
Weight, kg	45.0 ± 11.6	51.2 ± 11.9	0.54
Height, cm	141.8 ± 8.9	152.4 ± 10.3[a]	1.13
Body mass index, kg/m^2	22.0 ± 3.7	21.7 ± 3.1	0.06
Subtotal body fat, %	30.7 ± 5.9	19.8 ± 6.1[a]	1.87
Subtotal body fat, kg	13.0 ± 1.5	9.6 ± 1.3[a]	2.38
Subtotal lean mass, kg	26.7 ± 5.9	35.5 ± 7.1[a]	1.39
Physical activity			
Sedentary PA, min/day	509 ± 83	473 ± 67	0.49
Light PA, min/day	229 ± 70	218 ± 44	0.20
Moderate PA, min/day	28 ± 8	30 ± 9	0.33
Vigorous PA, min/day	7 ± 3	8 ± 3	0.39
Total PA, min/day	265 ± 73	257 ± 49	0.12
Bone mineral density, g/cm^2			
Proximal femur	0.771 ± 0.087	0.840 ± 0.140	0.60
Integral femoral neck	0.725 ± 0.070	0.778 ± 0.124	0.53
Trochanter	0.575 ± 0.065	0.643 ± 0.111	0.75
SL neck	0.645 ± 0.087	0.687 ± 0.127	0.39
IM neck	0.793 ± 0.084	0.854 ± 0.127	0.58
IM neck BMD/SL neck BMD	1.242 ± 0.166	1.254 ± 0.101	0.08
Tanner stage (I/II/III/IV/V)	(2/2/1/2/5)	(0/1/0/4/9)	–

PA, physical activity; SL, superolateral; IM, inferomedial. [a]$p < 0.05$ for differences between genders.

fat percentage and mass and lower lean body mass than males ($d = 1.1$–2.3; $p < 0.05$). There were no differences between the genders regarding age, body weight, body mass index and minutes on PA intensities ($p > 0.05$).

For BMD variables, no differences were found between groups, either in unadjusted (Table 1) or in adjusted models (data not shown, all $p > 0.05$). Effect size estimations were medium ($d = 0.3$–0.7) in the first model but they became lower in the adjusted model after applying the Hedges's corrections ($g = 0.01$–0.37).

Table 2 displays the BMDs for the two PA groups. HIGH DS females had increased integral and superolateral femoral neck BMDs (14.1% and 17.0%, respectively) in comparison with LOW DS females ($p < 0.05$; Hedges's $g = 1.6$). Despite not being significantly different, the BMDs of the proximal femur, trochanter and inferomedial regions were also increased in HIGH females (from 10.6% to 14.3%) when compared to LOW females; the differences showed large Hedges's g values (from 0.7 to 0.9).

Table 2: Bone mineral density (g/cm^2) values adjusted for age, body weight and height according to gender and physical activity (PA) groups (mean ± standard deviation).

Bone mineral density, g/cm^2	Females				Males			
	Low PA	High PA	η_p^2	Dif., %	Low PA	High PA	η_p^2	Dif., %
Proximal femur	0.732 ± 0.092	0.810 ± 0.092	0.776	10.6	0.826 ± 0.131	0.854 ± 0.131	0.199	3.4
Integral femoral neck	0.678 ± 0.054	0.774 ± 0.054[a]	1.626	14.1	0.796 ± 0.105	0.761 ± 0.105	0.312	4.4
Trochanter	0.537 ± 0.075	0.614 ± 0.075	0.936	14.3	0.614 ± 0.114	0.672 ± 0.114	0.475	9.4
Superolateral neck	0.595 ± 0.058	0.696 ± 0.058[a]	1.604	17.0	0.700 ± 0.124	0.676 ± 0.124	0.181	3.4
Inferomedial neck	0.742 ± 0.095	0.845 ± 0.095	0.999	13.9	0.872 ± 0.104	0.838 ± 0.104	0.306	3.9
IM neck BMD/SL neck BMD	1.257 ± 0.184	1.229 ± 0.184	0.140	2.2	1.258 ± 0.146	1.251 ± 0.146	0.045	0.6

SL, superolateral; IM, inferomedial. [a]$p < 0.05$ for differences between the PA groups of the same gender. η_p^2, partial eta squared, effect size: <0.01, small; 0.06, moderate; >0.14, large.

The unadjusted model showed that DS males in the LOW group had higher integral, superolateral and inferomedial femoral neck BMDs when compared with DS males in the HIGH group (data not shown), but these differences disappeared when BMD values were adjusted (Table 2; all $p > 0.05$).

Discussion

This cross-sectional investigation analyzed BMDs at different regions of the proximal femur and how the PA levels are related to the bone mass distribution in adolescent males and females with DS. To our knowledge, this is the first investigation analyzing the effect of PA on the BMD distribution at different regions of the femoral neck in subjects with DS. The main findings were that DS females of the HIGH group had increased integral and superolateral femoral neck BMDs when compared to DS females of the LOW group. In males, no differences were found between the two PA groups for any BMD variable.

The results suggest that physically active females with DS have a better relative mineralization of the neck region most likely associated with strong trabeculae in the secondary compressive bundle.

The importance of PA for the mineralization of growing bone [38] is well known. Besides, structural improvements can be achieved by increasing the mechanical loading via PA [39]. Evidence for the effects of PA in persons with low BMD similar to those with DS is scarce [33]. Studies carried out for PA in persons with DS are related to the evaluation of PA patterns [28, 40] and the prevalence of sufficient PA [41]. A previous research by our team found that adolescents with DS with more daily accumulation of PA presented more favorable BMD Z-scores at the whole body, lumbar spine and specially at the integral femoral neck [12]. In the current investigation, the femoral neck was divided into the superolateral and the inferomedial regions to gain additional insight about the risk of cervical fracture [42]. Although the proximal femur and femoral neck are controversial regions to be measured [13], they are particularly relevant in persons with DS. Wu [43] suggests that the hip might be the first skeletal site presenting significant deficits in bone mass in preadolescents with DS. The investigation of the relative mineralization is important, as a femoral neck fracture is one of the most common causes of hip fractures and also the fact that low PA is associated with an increased risk of suffering a bone fracture of the femoral neck [44].

As compared with their counterparts without DS, adolescent females with DS have lower BMD values at the hip [33, 45]. In line with prior investigations, males and females with DS presented similar BMD values for proximal femur, neck and trochanter regions [33]. When comparing BMDs in adolescents with DS within each gender, it seems that females from the HIGH group presented better BMDs at the integral and superolateral femoral neck regions in comparison with females from the LOW group. However, these differences were not observed for males. Several factors could explain these results. First, although males presented an improved body composition compared to females, they presented similar total PA. It is possible that if differences in total PA or intensity had been greater in DS males of the HIGH and LOW groups, BMD differences would have emerged. Second, the benefits of PA in the axial and the appendicular skeleton of people with DS have been studied [20, 46, 47]. However, as pointed out by Ferry and colleagues [46], there might be a limited sensitivity of the mechanostat (a model that describes the bone growth and bone loss stimulated by mechanical loadings) due to disturbances in the activation of estrogen receptors as a consequence of the DS phenotype [48]. Third, despite not being significantly different, the youngest participants of this study were classified into the highest PA group. These results are in agreement with the general trend of decreasing PA levels with increasing age [28, 41, 49]. The reduction in PA levels could be accompanied by a lower muscle force gain, its influence being more marked in females than in males due to their reduced levels of testosterone [50]. Sexual dimorphism in body composition has also been reported in adolescents with DS [51]; indeed, Center and colleagues [11] identified DS as an independent risk factor for low BMD in women but not in men with intellectual disability. Females, and concretely females with DS, have a two-fold risk, and the implementation of evidence-based exercise programs seems crucial.

Considering the proximal femur's shape, the superior aspect of the neck may be at a high risk of fracture because it is a relatively unstimulated region by routine mechanical loading [52]. Baptista and colleagues [53] have shown that the hip axis length and the femoral neck width were bigger in males with DS than in females. It seems that females have a reduced femoral neck bone size with a narrower femoral neck. It has been found that even light PA is very important to maintain a good bone status [12]. Previous studies showed that the BMD increased after performing a progressive low-impact exercise in persons with Crohn's disease [54]. Nevertheless, analyzing the time spent in moderate to vigorous PA, females only achieved

35 min/day vs. 38 min/day by males; these daily accumulations are far from the necessary 78 min/day to increase the bone mass in non-DS adolescents [55].

This study is not exempt from limitations. First, the relationships between daily PA and BMD may have been underestimated as the mechanical loading relevant to the bone (muscle and impact forces from PA) was not quantified by the accelerometers; it was assumed that adolescents with more PA would have accumulated a greater osteogenic stimulus. Second, the risk of a Type II error (false negative concerning whether an effect exists) was increased because of the limited sample size of the study. It has to be acknowledged that recruiting participants becomes complicated when adolescents with DS are the target participants; even so, the sample size was similar to that in recent studies with this population [56, 57]. Also, it needs to be considered that only cross-sectional data are provided herein; therefore, some of the results about the attainment of the bone mass cannot be confirmed. It is possible that some of the participants in the study (Tanner 5) reached their peak bone mass; therefore, the data have to be interpreted with caution. Further studies, including follow-up data, might help to elucidate the results presented herein. The use of DXA technology, on the other hand, the objective evaluation of PA and the inclusion of both genders in the sample were the main strengths of this investigation.

In conclusion, females with DS accumulating more total PA presented higher BMDs at the integral and superolateral femoral neck regions when compared with their less active peers, a difference that was not observed in the DS males. These results highlight the importance of PA in females with DS to improve their BMD in order to promote bone health.

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