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Bone mineral density and lean muscle mass characteristics in children with Gaucher disease treated with enzyme replacement therapy or untreated

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1. Introduction

Gaucher disease is a rare autosomal recessive lysosomal storage disorder with a predilection for type 1 with relatively milder disease expression among Ashkenazi Jews because of the presence of the N370S mutation [1]. Age of onset is variable as are the visceral organs affected and the severity and progression of involvement. Availability of disease-specific enzyme replacement therapy (ERT) for the past 25 years [2], has afforded effective improvement in hematological parameters and reduction in hepatosplenomegaly.

Nevertheless, prevention of bone-related adverse events such as osteoporosis, pathological fractures/deformation, and osteonecrosis remains a clinically meaningful unmet need [3] and for which, to date there are no good prognostic markers [4]. The single hint gleaned from bone densitometry, (by Dual Energy X-ray Absorptiometry; DXA) studies, is that lumbar spine bone density was a risk factor for fractures of the femur and spine in patients with type 1 Gaucher disease [5].

From the general literature, it is becoming increasingly evident that bone and muscle function in concert, achieving and maintaining skeletal robustness [6], thereby warding off frailty that is associated with risk of fractures and other adverse bone events [7]. This interplay is not surprising since the strongest mechanical forces experienced by bones are induced by muscle contractions that in turn induce and sustain bone density. Thus, decreased muscle mass and strength (sarcopenia), leads to lower bone density (osteopenia/osteoporosis). Reduced muscle mass has been shown to be related to risk of falls while osteopenia and osteoporosis are factors that cause fractures due to falling. Indeed, it has been suggested that combining these two markers as "sarco-osteopenia" might identify higher-fracture-risk populations [8]. This too seems logical since there are multiple processes other than the progressive effects of age [9] that are common to sarcopenia and osteopenia such as sensitivity to reduced anabolic hormone secretion, increased inflammatory cytokine activity [10], the impact of type IIB muscle fibers [11], and reduced physical activity.

Recently the question has been raised whether the relationship between bone health and muscle fitness is mediated by lean muscle mass and whether that association already exists in children [12]. These queries highlight the findings that there is a differential profile in children with variously, bone and muscle diseases, relative to healthy children [13] based on interpretation of whole body DXA evaluations [14].

In children with type 1 (non-neuronopathic) Gaucher disease, it is known that skeletal disease is evident prior to treatment [15], that osteopenia may be a preeminent finding in adolescents [16], and that impaired growth potential which is common [17] may also be linked to risk of falls and fractures in adulthood [18]. However, bone mineral density (BMD), and lean muscle mass (LMM) have never been evaluated in children with type 1 Gaucher disease. The purpose of this study was to address the question of the utility of whole body DXA with evaluations of BMD, LMM, and fat fraction (FF) in children with Gaucher disease to assess the potential of DXA as a measure of bone-muscle relationships for prognostication of adverse skeletal events in these pediatric patients.

2. Methods

All children aged 3 to 16 years who are monitored at the Gaucher Clinic at Shaare Zedek Medical Center in Jerusalem Israel undergo routine evaluations either annually or semi-annually. Whole body DXA had been added to the routine evaluations in the past few years approximately every-other-year for children older than three years of age (the lower limit for normal values) as recommended for adults as per international guidelines [19].

Evaluation by DXA scan, with calculation of LMM, FF and BMD for the whole body and for specific regions of interest (such as the femoral neck, and lumbar spine) was performed (Hologic, Discovery QDR) by a

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Table 1
Demographic characteristics of the cohorts (ERT = enzyme replacement therapy; BMI = body mass index; BMD = bone mineral density; LMM = lean muscle mass; FF = fat fraction).

		Compound heterozygotes (72.9%)			
	All patients	Treated	Untreated	All	Homozygous N370S/N370S (27.1%)
Number	48	26 (74.3%)	9 (25.7%)	35	13
Males:females	24:24	11:15	2:7	13:22	11:2
Genotypes*: N370S/N370S:N370S/other:other/other	13:25:10	0:18:8	0:7:2	0:25:10	13:0:0
Type 3 patients	6 (12.5%)	5 (19.2%)	1 (11.1%)	6 (17.1%)	0
Mean age at advent ERT (range) in years	–	5 (2–10.5)	–	–	–
Mean (range) ERT in years	–	5.8 (1−13)	–	–	–
ERT dosage (units/kg/EOW)	–	1@15 units; 14@30 units; 11@45–60 units	–	–	–

*N370S/other = N370S/84GG (7); N370S/L444P (6); N370S/R496H (3); N370S/IVS2 + 1 (2); N370S/C342Y (2); N370S/M85T (1); N370S/R395P (1); N370S/C112Z (1); N370S/V394L (1); N370S/other (1).
Other/other = L444P/D409H (3); D409H/D409H (3); V394L/L444P (2); 84GG/T431 (1); L496H/RecTL (1).

single technician (MT). For the above reasons, and because this study was not designed to be used as a predicator of management, a waiver for Informed Consent was provided by the local Helsinki Committee (Institutional Review Board).

In addition to demographic characteristics, Gaucher disease parameters including growth curves, and investigation of comorbidities that might impact bone or muscle development, routine blood biochemistry and hematology results were evaluated.

Children who had been receiving at least one year of ERT, regardless of which type and at which dose, were considered "treated" even if treatment began before the age of three years. Moreover, dosage was considered a constant since it is weight adjusted.

DXA outputs included bone mineral content (BMC), BMD of the whole body (excluding head), lumbar spine (LS) and femoral neck (FN). z-scores were calculated according to age. LMM and FF were calculated by the software relative to CDC healthy controls [20]. The latter employed height and weight measurements and body mass index (BMI) as performed at the same time as the DXA examination.

2.1. Statistical analysis

The Chi-square, Student's *t*-test and Pearson correlations as well as one-way ANOVA were employed to compare independent variables and categorical/numerical variables and linear relationships between groups.

3. Results

Table 1 presents the demographic data (including genotype, phenotype, gender, and ERT status) of children in the current study. Forty eight children were evaluated, 35 (72.9%) patients were compound heterozygotes of whom 26 (74.3%) children were treated with ERT whereas none of the children ($n = 13$) who were homozygous N370S/N370S (milder disease as determined by AZ) are treated with ERT.

Evaluation of DXA finding is based on whole-group findings and division into the three treatment status groups as described above. Table 2 summarizes the findings of the current study. BMI values were within normal limits for all the children but most children were in the low range. Age adjustment of BMI (percentiles of CDC normal BMI curves), reveals only three patients (one in each group) where BMI was below the 25th percentile. When comparing means of whole body BMD z-scores, of all treated children (all of whom are heterozygous) to all untreated children (heterozygotes and homozygotes), it was significantly higher ($P = 0.007$). This significant difference was not seen in either the comparison of means of FN or LS BMDs.

For the whole group, there was a significant positive linear correlation between age and BMD as expected ($R^2 = 0.69–0.88$). However, absolute BMD values were seen to be low, i.e., in the area of osteopenia, with a weak linear correlation ($R^2 = 0.30$) of z-score to age. Fig. 1 demonstrates the linear correlation with age for each group (based on genotype and treatment status) with regard to whole body BMD. The linear correlation line has a similar trend in the homozygote group (non-treated, milder disease) as the treated heterozygotes, while the untreated heterozygotes do not show a comparable pattern. Similar graphs were generated for LS and FN correlations (not shown) albeit the absolute BMD values for FN in particular were closer to normal while the linear correlation coefficients were weaker.

Fig. 2 presents the correlations between age and LMM for all subgroups. Results are similar to those seen for BMD other than that for the untreated heterozygotes where there was a trend to increasing values with age.

Fig. 3 shows the comparison of FF in the entire group. There was a weak correlation of FF and age; it reflects the weak correlations of the sub-groups as well, although it was weakest among the treated heterozygotes. When assessing only the treated heterozygotes subdivided by gender, the positive correlation coefficient albeit moderate for girls only, was weak for both genders relative to age.

Fig. 4 illustrates that LMM and bone mineral content (BMC) were closely correlated ($P < 0.005$), as was expected. Both evaluators are

Table 2
Differences of BMI and DXA between cohort groups.

		Compound heterozygotes				
	All patients	Treated	Untreated	All	Homozygous N370S/N370S	*P* values*
Mean BMI (range)	16.8 (14.2–23.9)	17.7 (15–23.9)	15.6 (14.2–16.9)	17.1 (14.2–33.9)	16 (14.3–19)	$P = 0.03$
Mean BMI percentile (range)	45.2 (7–92)	49 (7–92)	44 (7–80)	47.7 (7–92)	38.3 (8–76)	$P = 0.417$
Mean lumbar spine BMD ± SD	0.59 ± 0.13	0.61 ± 0.13	0.52 ± 0.1	0.59 ± 0.13	0.60 ± 0.12	$P = 0.227$
Median ± SD lumbar spine z-score	−0.85 ± 1.03	−1.1 ± 0.96	−1.0 ± 1.25	−1.1 ± 1.02	−0.3 ± 0.9	$P = 0.061$
Mean femoral neck BMD ± SD (range)	0.68 ± 0.1	0.70 ± 0.12	0.62 ± 0.03	0.68 ± 0.11	0.69 ± 0.07	$P = 0.370$
Median ± SD femoral neck z-score	−0.90 ± 1.07	−1.1 ± 1.04	−0.70 ± 0.56	−1.0 ± 0.97	−0.2 ± 1.30	$P = 0.266$
Mean whole body BMD ± SD (range)	0.75 ± 0.11	0.78 ± 0.11	0.65 ± 0.06	0.75 ± 0.12	0.75 ± 0.01	$P = 0.007$
Median ± SD whole body z-score	−1.4 ± 1.29	−1.4 ± 1.62	−1.9 ± 0.84	−1.5 ± 1.46	−0.95 ± 0.59	$P = 0.504$

* By 1-way ANOVA (CI 95%).

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