Evaluation of bone health in patients with mucopolysaccharidosis

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Abstract

Introduction: This study aimed to evaluate the relationship between clinical findings, height and weight standard deviation scores, 25-hydroxyvitamin D_3 ($25(OH)D_3$) level, and dual-energy x-ray absorptiometry (DXA) results in patients diagnosed with mucopolysaccharidosis (MPS), where effective current treatments such as enzyme replacement therapy (ERT) can be accessed.

Materials and Methods: $25(OH)D_3$ level was measured in 126 patients with MPS (17 with MPS I, 14 with MPS II, 18 with MPS III, 33 with MPS IVA, and 44 with MPS VI; 24–524 months). DXA was performed in 45 of these patients (8 with MPS I, 4 with MPS II, 4 with MPS III, 12 with MPS IVA, and 17 with MPS VI; 62–197 months; all patients were under 18 when DXA was performed) to assess bone mineral density (BMD) of the lumbar spine.

Results: In total, 67.5% patients had a short stature, and 50% of them were underweight for their age. Of the patients, 13.5% were immobile, 28.6% had $25(OH)D_3$ deficiency, and 30.2% had an insufficient level of $25(OH)D_3$. BMD z-score of 45 patients was -2.5 ± 1.7. In 40% patients, it was <-2. However, after correction for height-for-age z-score (HAZ), HAZ-adjusted BMD z-score was -0.1 ± 0.9. In 2.2% patients, it was <-2.

Conclusion: The low BMD z-score prevalence reported with DXA was misleadingly higher in children with MPS and short stature. To prevent exposure to unnecessary antiresorptive treatments in these children, the effect of severe short stature and bone geometry on DXA measurements should be considered; further studies on bone health are warranted.

Keywords: Mucopolysaccharidosis, $25(OH)D_3$, bone mineral density, skeletal system, dysostosis multiplex

Introduction

Mucopolysaccharidoses (MPS) are a group of lysosomal storage diseases characterized by chronic, progressive, and multi-system involvement, which develop due to deficiencies of enzymes required for breaking down glycosaminoglycans (GAG), which are structural components of connective tissue, such as dermatan sulfate, heparin sulfate, keratan sulfate, chondroitin sulfate, and hyaluronic acid. The general prevalence of MPS is approximately one in 25000 live births. It has seven subtypes according to the deficient enzyme. The intracellular accumulation of GAGs that could not be broken down causes progressive damage and leads to clinical manifestations in joints and bones, as well as in multiple organs and systems such as the central nervous system, eye, lung, heart, liver, spleen, kidney, and connective tissue [1]. Bone and joint findings that are known to affect the quality of life in patients with MPS include short stature, posture abnormalities, short neck, pectus carinatum/excavatum, kyphosis, scoliosis, joint restriction/laxity, genu valgum/varum, carpal tunnel syndrome, and hip dislocation.

Since bone is a dynamic organ with a fast turnover, it can be affected by all events that occur during the mineralization process. The development of bone mass and density begins in the intrauterine period and ends in the 30s in healthy individuals. In studies conducted on animals with MPS, it has been shown that increasing GAG accumulation in chondrocytes starting from the intrauterine period plays a role in the physiopathology of the effect on bone growth and mineralization, and this accumulation impairs bone formation and remodeling [2,3]. It is not clear whether the abnormalities observed in these models cause osteoporosis or an increased risk of fractures in patients with MPS. It is considered that inadequate nutrition and sunlight intake, limited effort capacity due to cardiac and respiratory involvement, less than optimal physical activity level due to pain and joint contractures/laxity may lead to decreased bone density [4]. However, studies on the evaluation of bone mineral density (BMD) in patients with MPS are limited [2-6]. Therefore, we evaluated BMD via Dual-energy X-ray absorptiometry (DXA) in patients with different types of MPS. It is also difficult to correctly evaluate BMD by using DXA in children with short stature. Correct evaluation is very important in these patients to avoid unnecessary exposure to antiresorptive treatments. For this reason, the patients were evaluated in two different ways according to their height and Zemel et al. [7] method

for height-for-age z-score (HAZ). Cross-sectional measurements were performed in some of our patients, and DXA measurements were made before and after enzyme replacement therapy (ERT) in order to understand the effect of ERT on bone health in others.

An important indicator of bone health is the 25-hydroxyvitamin D_3 ($25(OH)D_3$) level. However, there is limited information in the literature about the $25(OH)D_3$ level and the factors affecting it in MPS. Based on the idea that GAGs accumulated in the gastrointestinal system and liver in MPS may impair the metabolism and absorption of $25(OH)D_3$ in addition to its inadequate intake, absorption, and use, which are known to play a role in many chronic diseases, $25(OH)D_3$ levels were measured in our patients. In addition, the relationship between $25(OH)D_3$ levels, DXA results, and clinical findings was evaluated.

The present study is a large-scale bone health assessment conducted in a large number of patients with various types of MPS.

Materials and methods

In this study, the files of patients who were diagnosed with MPS by enzyme level and mutation analysis and followed up in the Department of Pediatric Metabolism and Nutrition Outpatient Clinic of Çukurova University Faculty of Medicine were analyzed retrospectively. In total, 126 (55 girls and 71 boys) patients with MPS were included in the study. Ethics committee approval was obtained from the "Non-Invasive Clinical Research Ethics Committee of Çukurova University Faculty of Medicine" for the study, and informed consent forms were obtained from all of the subjects. MPS types, growth criteria, joint findings, mobility level, presence of fractures; serum calcium, phosphorus, alkaline phosphatase, $25(OH)D_3$ levels; and DXA results were recorded from the patient files. Height and weight standard deviation scores (SDS) were calculated according to standard growth tables prepared for Turkish children [8]. The patients were evaluated in three groups; those with a body weight SDS <-2 were defined as underweight for their age, those with a body weight SDS between -2 and $+2$ as normal body weight for their age, and those with a body weight SDS $>+2$ as overweight (short stature) for their age. Patients with a height SDS <-2 were considered short, and those with a height SDS >-2 were considered normal. BMD measurements for the lumbar spine (L1-L4) were obtained using DXA

(QDR 4500, Hologic Inc., Bedford, MA, USA). Patients who received bisphosphonate therapy when DXA analysis were done were excluded from this study.

BMD z-scores were evaluated according to age. In addition, BMD z-scores were adjusted for HAZ according to the model by Zemel et al [7] to make a correction for height deficits observed in patients with MPS. According to the definition of the Official Positions of the International Society for Clinical Densitometry, a z-score of ≤−2.0 was defined as “below the expected range for age,” and a z-score >−2.0 was regarded as "within the expected range for age” [9].

Plasma 25(OH)D_3 levels were measured by High Performance Liquid Chromatography (HPLC) method with Shimadzu HPLC Prominence System (Shimadzu Inc., Kyoto, Japan) fully automated auto analyzer using kits of Immu Chrom GmbH (Heppenheim). According to the consensus report published by the European Society for Pediatric Endocrinology (ESPE) in 2016, 25(OH)D_3 levels were defined as normal for > 20 ng/ml, insufficiency for 12–20 ng/ml, and deficiency for <12 ng/ml [10].

Statistical analysis

Categorical measurements were summarized as numbers and percentages, frequency and ratio values and continuous measurements as mean and standard deviation (minimum-maximum where appropriate). The distribution of variables was measured with the Kolmogorov-Smirnov test. Kruskal-wallis, mann-whitney u test was used in the analysis of quantitative independent data. Pearson Chi-square and Fisher exact test statistics were used to compare categorical variables. Shapiro-Wilk test was used to determine whether the parameters in the study showed normal distribution. In comparison of continuous measurements between groups, distributions were controlled, and independent student's t-test was used in paired group analyses. Statistical significance level was taken as 0.05 in all tests. Data analysis was performed using SPSS software version 27.0 for Windows (IBM Corporation, Armonk, NY, USA).

Results

The data of 126 patients, including 55 (43.7%) girls and 71 (56.3%) boys, whose bone health was evaluated, out of 216 patients diagnosed with MPS in the Department of Pediatric Metabolism and

Nutrition at Çukurova University Faculty of Medicine, were analyzed. When patients were evaluated according to MPS types, 17 (13.5%) had type I, 14 (11.1%) had type II, 18 (14.3%) had type III, 33 (26.2%) had type IVA, and 44 (34.9%) had type VI. The age at diagnosis of the patients with MPS was 60.97 ± 53.9 (0–239) months, the duration of disease was 76.4 ± 50.4 (17–454) months, and their mean current age was 133.60 ± 72.2 (24−524) months. Parental consanguinity was present in 100 patients (79.4%) and family history was present in 63 patients (50%; Table 1). In total, 47 (21 families) of 126 patients from 100 families included sibling and cousin cases.

Short stature was detected in 85 (67.5%) patients with MPS. The mean height SDS of these patients was −4.26 ± 3.5 (min: −13.43, max: 1.69). While short stature had the highest prevalence in type IVA, it had the lowest prevalence in type III. Of the patients, 63 (50%) were underweight for their age, 61 (48.4%) had normal weight for their age, and 2 (1.6%) were overweight for their age. The mean body weight SDS was −2.66 ± 2.9 (min: −13.44, max: 3.28). Two overweight patients had MPS type II. Normal body weight for age was most common in type II and type III and least common in type IVA (Tables 1).

Of the patients, 50.8% (64/126) had pain originating from the skeletal system. Pain was most common in MPS type IVA and type VI. The pain was located, in order of frequency, in the lower and upper extremities, hips, back, and waist. Seventeen (13.5%) of the patients were immobile. When immobile patients were classified according to MPS types, 10 (58.8%) had MPS type IVA, 3 (17.6%) type III, two (11.8%) type II, and two type I. Fracture was present in only 1 (0.79%) patient with MPS type IVA and occurred after a minimal trauma.

The mean 25(OH)D_3 level of all patients was 18.61 ± 10.5 (1.69–68) ng/mL. Deficiency or insufficiency was detected in 74 patients (58.7%). There was deficiency (7.53 ± 2.3 ng/mL) in 36 patients (28.6%), and 38 (30.2%) patients had insufficiency (15.90 ± 2.2 ng/mL). While mean 25(OH)D_3 level was 18.82 ± 10.3 in patients with short stature, it was 18.17 ± 11.0 ng/mL in those with normal height, and there was no statistically significant difference between them ($p = 0.746$). None of our patients had a history or signs of chronic diarrhea or malabsorption. 25(OH)D_3 level was normal in 21 (33.3%) of the patients who were underweight for their age, while it was found to be low in 42 (66.7%) of them. While the 25(OH)D_3 level was normal in 31 (49.2%) patients who were not

underweight for their age, 32 (50.8%) of them had low levels. Although 25(OH)D_3 levels were found to be lower in patients who were underweight for their age, this difference was not statistically significant ($p = 0.20$). Two type III patients had a gastrostomy. One of them had a normal 25(OH)D_3 level and the other had a deficient level. Fourteen (82.4%) immobile patients were underweight for their age, and 25(OH)D_3 levels were below normal limits in 12 (70.6%) of them. Although the mean 25(OH)D_3 level in immobile patients (15.96 ± 8.97) was lower than in mobile patients (19.02 ± 10.65), no statistically significant difference was observed between them ($p = 0.264$). 25(OH)D_3 levels in different MPS types are given in Table 1. The lowest level of 25(OH)D_3 was observed in patients with type III and type IVA. Although 25(OH)D_3 levels varied among all types, this value was not statistically significant ($p = 0.807$). When an evaluation was made according to gender, it was observed that there was no difference in terms of 25(OH)D_3 levels. Calcium, phosphorus, and alkaline phosphatase levels were normal in all patients according to age and gender [11-12].

Of the patients, 94 (74.6%) were receiving ERT. None of the type III patients were receiving ERT since it was not an approved treatment, and 14 of the type IV patients were not receiving ERT since they could not meet the reporting criteria in Turkey. Those who received ERT, the age at which they started receiving ERT, and duration of treatment according to MPS subtypes are presented in Table 2.

During follow-up of the patients, at the time when 25(OH)D_3 level was measured, DXA was performed in 45 patients within the age range of 5–17 years; 19 of these patients (42.2%) were girls and their mean age was 122.53 ± 33.0 (68–182) months, 26 of them (57.8%) were male and their mean age was 113.85 ± 42.5 (62–197) months at the time of the DXA scan. DXA z-score was <-2 in 27 (60%) of the patients. When an evaluation was made according to types, it was observed that the effect on BMD was determined to be the highest in type IVA and type VI, which had the shortest stature, and it was observed to be the lowest in type III and type II where short stature was less common. The DXA z-score results of the patients according to the types are given in Table 3. Height SDS of all of the patients who underwent DXA was <-2. However, when a correction was made for height age, no evaluation could be made according to the height age, since the device used could not make any measurements in children aged <5 years and the height age of most of the patients were <5 years. Therefore, while interpreting the DXA results, the results were re-evaluated using the pediatric bone

density calculator prepared by Zemel et al. [7]. When analyzed according to HAZ, it was observed that the rate of DXA z-score being <−2 decreased from 60% to 2.2% (1/45). Thirty of 45 patients had received ERT for 57.43 ± 31.7 (12–108) months before DXA. When the Z-scores of those who received and did not receive ERT were compared, it was observed that the DXA Z-scores of those who received ERT (−2.5 ± 1.8) were not statistically significantly different from those who did not receive ERT (−2.6 ± 1.6) ($p = 0.876$). Interestingly, while the mean 25(OH)D_3 level of the patients who received ERT was 20.60 ± 13 ng/mL, it was 18.5 ± 7.8 ng/mL for those who did not receive it ($p = 0.857$). Even if this difference was not statistically significant, it brought to our mind the question of whether ERT affects the production of 25(OH)D_3 through the skin. General characteristics, DXA results, and 25(OH)D_3 levels of 45 patients who were evaluated with DXA are given in Table 4.

The mean 25(OH)D_3 level of the patients in whom DXA could be performed was 19.89 ± 11.45 (3.5–68) ng/mL. While the 25(OH)D_3 level was 18.1 ± 9.2 in patients with an age adjusted DXA Z-score below normal, it was 22.59 ± 14.0 in those with a normal DXA Z-score. Although 25(OH)D_3 level was found to be lower in those with a DXA Z-score below normal, the difference was not statistically significant ($p > 0.05$). All patients with a low score in DXA had varying degrees of pain. However, statistical evaluation could not be made, because pain was a subjective finding and the patients could not fully describe the characteristics of their pain.

Discussion

Although bone and joint findings in different types of MPS are important components of the clinical presentation and have a direct effect on quality of life and prognosis, there are limited studies on this subject. Similarly, there are also limited data on 25(OH)D_3 levels and BMD in patients with MPS. The aim of this study was to evaluate the relationship between clinical findings, height and weight SDS, 25(OH)D_3 level, and DXA results in patients with different types of MPS, where effective current treatments such as ERT can be accessed. As far as we have investigated during the literature review, this study is the first single-center large data sharing on the subject in a large number of patients with different types of MPS.

In a study conducted by Lin HY et al. [13] with 30 MPS (2 type I, 12 type II, 2 type IIIB, 9 type IVA, and 5 type VI) patients, it was reported that short stature was found at a rate of 81% and lower body weight than expected for age at a rate of 31%. In a study published by Thomas et al. in 2014, 40 cases [20 type I-Hurler syndrome (IH), 6 type I Hurler-Scheie/Scheie (IHS/IS), 10 type II, and 4 type VI] between the ages of 5 and 16 were evaluated, and the rate of short stature was reported to be 55% [14]. In our study, 126 patients (17 type I, 14 type II, 18 type III, 33 type IVA, and 44 type VI) were evaluated, and short stature was found at a rate of 67.5% and lower body weight than expected for age at a rate of 50%. Interestingly, two type II patients in our study were overweight for their age. It was considered that these differences in height and body weight were due to differences in the number of patients and MPS types in the three studies.

In a study by Lin HY et al. [13], skeletal pain in MPS was reported at a rate of 43%. In our study, this rate was 50.8%. The reason for the higher rate of pain originating from the skeletal system in our case series was considered to be the fact that the rate of patients in types I, IVA, and VI subgroups was 74.6% in our study, whereas this rate was lower (50.3%) in the other study.

Bone mass development is positively affected by physical activity, calcium, $25(OH)D_3$, and adequate protein intake. However, inadequate hip rotation, limited mobility, and reduced physical activity of patients with MPS due to joint contractures cause an increased risk of insufficient bone mineralization. In 2014, Thomas et al. reported that there were fractures after falling in two (5%) patients, for whom they did not specify the subgroup, in their series of 40 cases [13]. In a small series of eight patients with MPS (four type VI and four type II) in California, a history of shoulder fracture after falling from a bunk bed was reported in one type II MPS patient (12.5%) [4]. Apart from these, a right femoral neck stress fracture was reported in a 20-year-old type VI patient [15], and a left femoral neck fracture with minimal trauma in a 12-year-old male patient with type II [16]. In our study, a fracture was detected after a fall in a MPS type IVA patient (0.8%) with multiple thoracolumbar stage 2 compression fracture ($25(OH)D_3$ level: 44 ng/mL and lumbar vertebra z-score: −5.1) in the third year of treatment.

In epidemiological studies conducted in different parts of the world, $25(OH)D_3$ deficiency was reported at a rate of 7-68% and $25(OH)D_3$ insufficiency at a rate of 19-61% in healthy children and

adolescents [17]. In Turkey, the overall prevalence of 25(OH)D_3 deficiency was reported to be 8-61% in children and adolescents, varying with age, gender, and seasons [18]. In a study conducted between 2008 and 2010 in 440 children and adolescents aged 0-16 years without chronic disease, 25(OH)D_3 deficiency/insufficiency was found at a rate of 40%, and it was reported to be higher in girls than in boys [19]. In our study no difference was found between genders in 25(OH)D_3 deficiency.

25(OH)D_3 deficiency is common in chronic diseases such as chronic liver disease, chronic renal failure, vitiligo, celiac disease, cystic fibrosis, inflammatory bowel diseases, in cases of anticonvulsant and antifungal medication use, receiving chronic steroid therapy and long-term hospitalization, due to inadequate sunlight intake as well as impairments in the synthesis and metabolism of 25(OH)D_3 [17]. In a study conducted with patients who presented to the pediatric endocrinology outpatient clinic with different diagnoses, 25(OH)D_3 deficiency was found at a rate of 51.5% and insufficiency at a rate of 35.1%. In the same study, it was reported that the rate of 25(OH)D_3 deficiency/insufficiency was 87% in obese patients, and 83% in patients who were followed up due to hypothyroidism, short stature, growth hormone deficiency, congenital adrenal hyperplasia, and puberty problems [20]. Since the rate of 25(OH)D_3 deficiency/insufficiency was in a very broad range in all of these studies, we considered that it would be more appropriate to make a comparison with studies conducted in different chronic patient groups under the same climatic conditions. There are two studies in which 25(OH)D_3 levels were measured in different patient groups in our city. In a study conducted with chronic liver patients, deficiency/insufficiency of 25(OH)D_3 levels was found at a rate of 48% and it was found at a rate of 31.8% in type 1 diabetes patients [21,22]. In the present study, we found 25(OH)D_3 deficiency at a rate of 28.6%, insufficiency at a rate of 30.2%, and decreased levels of 25(OH)D_3 in total at a higher rate of 58.8% in different types of MPS. This made us believe that sun rays may not be the main factor in deficiency or insufficiency of 25(OH)D_3 in MPS. Although there are limited publications on 25(OH)D_3 levels in patients with MPS, the rate of low 25(OH)D_3 levels (<30ng/mL) was found to be 87.5% in 8 patients with MPS (4 type VI and 4 type II) in California. As this rate was 31% in healthy local controls, it was reported that the decrease in patients with MPS was much higher. Similar to our study, they reported that this rate was 50% when the 25(OH)D_3 deficiency/insufficiency level was taken as <20ng/mL [4]. On the contrary, in another study conducted with 40 cases with different MPS

types, low 25(OH)D_3 was reported in only three (9%) patients [14]. In a study conducted in Turkey, 25(OH)D_3 levels were measured only in 15 MPS type III patients and the deficiency/insufficiency rate was 60% (mean 25(OH)D_3 level: 22.4 ± 12.9 ng/mL) [23]. In our study on 25(OH)D_3 level in our patient group with the largest number of patients with different types of MPS in the literature, we found the deficiency/insufficiency rate to be 58.8%; when we assumed the 25(OH)D_3 level as 30 ng/dL, we found a higher rate of 87.5%. We considered that MPS posed a risk for low 25(OH)D_3, since the number of our patients was significantly higher than other studies. 25(OH)D_3 level was low in 70.6% of the immobile patients. It was considered that the reason for low levels being more common in immobile patients than in the whole group might be due to insufficient exposure to sunlight. When evaluated according to types, it was considered that the reason for having found the highest rate of low 25(OH)D_3 level in type III and type IVA might be the neurological findings in type III and the difficulty in leaving the house due to immobility in type IVA. The reasons for the higher rate of low 25(OH)D_3 level, which is known to be low in chronic systemic diseases, in our study were considered to be GAGs accumulated in the skin reducing UV rays and GAGs accumulated in the small intestine reducing absorption of vitamin D_2 and D_3 in MPS. However, more comprehensive studies are needed to fully elucidate the physiopathology. Based on this result, it was concluded that although patients with MPS are not among the risk groups defined for 25(OH)D_3 prophylaxis, routine monitoring of 25(OH)D_3 levels is required in these patients.

It is well known that many children with chronic diseases are at risk for low bone mass [24-29]. Patients with MPS are at risk of low BMD, because they are known to have both chronic diseases and problems with bone growth and mineralization from animal experiments and it has been shown that increasing GAG accumulation in chondrocytes starting from the prenatal period may play a role. However, the number of studies on this subject is very limited.

In a study conducted with 15 MPS type III patients in Turkey, it was reported that osteoporosis (13%) and osteopenia (7%) were found at a rate of 20% [23]. In our study, it was observed that four of the type III patients underwent DXA, and 25% of them had osteopenia and 25% osteoporosis.

Fung et al. [4] evaluated four patients with type II and four with type VI who received ERT, and reported that after correcting the DXA z-score according to HAZ, it was found to be within the normal

range for all patients except one (12.5%), but DXA could not be performed before ERT and thus they could not fully interpret the effects of ERT on bone mineralization. Similarly, when we evaluated 30 patients (8 type I, 4 type II, 2 type IV, and 16 type VI) who received ERT at the time of DXA scan, we found that DXA z-score was 56.7% before correction for HAZ, whereas it was lower (0%) after the correction.

In a study evaluating the DXA measurements of 40 MPS (20 MPS IH, 6 MPS IHS/IS, 10 MPS II, and 4 MPS VI) patients (it was reported that hematopoietic stem cell transplantation was performed in all MPS I-H patients aged <3 years and in two type VI patients, while the other patients received ERT) the prevalence of low BMD was found to be 48% for lumbar vertebra, and when they evaluated the same data according to bone age, there was not a significant change in this rate (36%), but the rate of DXA z-score being <−2 was reduced to 6% after correction for HAZ. Therefore, it was emphasized that this should definitely be taken into account in children with short stature, and DXA should be evaluated by adjusting not only for height but also for HAZ [14]. When we examined our 45 patients, we found the prevalence of low BMD for lumbar vertebra to be 60%, and similarly 2.2% after correcting for HAZ. This result reminded us once again that height, age, and gender maturation should also be taken into account when evaluating DXA in order to prevent unnecessary antiresorptive treatment in patients with MPS.

In conclusion, our study had some limitations despite the large number of patients included. The age range of the patients was broad, and the numbers of patients with different MPS types were not similar. The effect of puberty could not be ruled out. $25(OH)D_3$ deficiency was found to be at a higher rate than in other studies. Low BMD for chronological age and gender in children with MPS was demonstrated once again with this study. In addition, it was observed that adjustment for HAZ was more appropriate due to abnormal bone development in addition to short stature, and our data were consistent with the literature after this correction. As a result of this evaluation, we have demonstrated that the low BMD z-score prevalence reported with DXA in children with MPS was incorrectly evaluated as high.

Author contributions: DK, NOM: conceptualization, methodology, and writing original draft. DK, NOM, FDB, SK, BK, EK: methodology and software DK, NOM, FDB, SK, BSY, OK, SB: conceptualization and writing. GS: Statistical analysis. DK, NOM, FDB: review and editing. All authors contributed to development and critical review of the manuscript.

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Declarations

Conflict of interest The authors report no conflict of interest related to this work.

Ethical approval All procedures involving human participants were performed in accordance with the ethical standards of the institutional and/or national research committee, in addition to the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

Consent for publication This manuscript has been approved by all the co-authors and has not been published before.

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Tables

Table 1. MPS subtypes, auxological data, mobility, and bone health parameters at the time of diagnosis

	n (%)	Consanguinity	Family history	Age (month)	Height SDS	Weight SDS	25(OH)D_3 ng/mL	Those with a short stature	Those with low weight	Those who are immobile	Those with 25(OH)D_3 deficiency	Those with 25(OH)D_3 insufficiency
	N			Mean ± SD (min–max)				n				
Type I	17 (13.5%)	14	8	32.88±41.4 (0-179)	-3.36±2.7 (-7.57/0.55)	-1.88±1.4 (-4.66/-0.01)	21.59±14.9 (7.6-68)	11	7	2	5	3
Type II	14 (11.1%)	4	3	35.71±20.9 (1-67)	-1.23±1.9 (-4.37/1.69)	0.38±1.6 (-2.05/3.28)	19.62±12.0 (4.3-45.6)	5	2	2	5	2
Type III	18 (14.3%)	17	8	78.94±50.0 (20-175)	-1.82±1.5 (-5.49/0.82)	-0.85±2.1 (-8.45/1.08)	16.48±9.0 (4.8-42.6)	6	3	3	6	5
Type IVA	33 (26.2%)	30	18	90.27±59.8 (4-217)	-7.48±3.5 (-13.43/-0.14)	-4.93±3.2 (-13.44/0.34)	17.41±9.2 (1.69-36.1)	31	25	10	9	13
Type VI	44 (34.9%)	35	26	50.52±50.9 (3-239)	-4,15±2.9 (-11/1.2)	-2.95±2.5 (-10.58/0.56)	18.91±9.5 (3.5-41.2)	32	26	0	11	15
Total	126 (100%)	100 (79.4%)	63 (50.0%)	60.97±53.9 (0-239)	-4.26±3.5 (-13.43/1.69)	-2.66±2.9 (-13.44/3.28)	18.61±10.5 (1.69-68.00)	85 (67.5%)	63 (50.0%)	17 (13.5%)	36 (28.6%)	38 (30.2%)

MPS: Mucopolysaccharidosis; SDS: Standard deviation score; 25(OH)D_3: 25-hydroxyvitamin D3

Table 2. Age at starting ERT and duration of treatment in patients receiving ERT

	Type I	Type II	Type IVA	Type VI	Total
Those who are receiving/not receiving ERT (n)	17/0	14/0	19/14	44/0	94/14
Age at starting ERT (months)	35,35±41,1	39,64±21,2	137,63±106,5	50,64±47,0	63,82±70,7
ERT duration (months)	82,41±29,1	88,43±36,3	54,47±11,9	74,05±35,5	73,74±32,6

ERT: Enzyme replacement therapy

Table 3. DXA z-score results according to MPS types

MPS type (n)	z-score according to chronological age Mean ± SD (min/max)	z-score according to HAZ Mean ± SD (min/max)
Type I (8)	-2.63±1.7 (-5.30/0.20)	-0.26±1.0 (-1.92/1.08)
Type II (4)	0.03±0.9 (-1.30/0.60)	-0.13±0.2 (-0.35/-0.01)
Type III (4)	-1.25±1.9 (-3.20/1.30)	-0.10±1.1 (-1.13/1.36)
Type IVA (12)	-3.30±1.3 (-5.50/-1.00)	0.16±1.27 (-3.11/1.54)
Type VI (17)	-2.85±1.55 (-5.50/-0.10)	-0.16±0.66 (-1.28/1.38)
Total (45)	-2.54±1.73 (-5.50/1.3)	-0.08±0.91 (-3.11/1.54)

DXA: Dual-energy X-ray absorptiometry; MPS: Mucopolysaccharidosis; SD: Standard deviation

Table 4. Characteristics of patients who underwent DXA

		Gender	Type	Short stature	Low weight	Mobility	Age at diagnosis (months)	Age at DXA (months)	Lumbar BMD z-score	Lumbar HAZ-adjusted z-score	25(OH)D₃ (ng/mL)
Those who were receiving ERT at the time of DXA scan	P1	M	VI	+	+	+	46	84	−1.90	0.98	13.5
	P2	M	VI	+	+	+	56	145	−2.80	−0.6	19
	P3	F	I	+	+	−	26	85	−4.30	0.16	8.9
	P4	M	VI	+	+	+	41	127	−3.40	−0.45	27.3
	P5	M	VI	+	+	+	23	72	−1.07	0.30	11.4
	P6	F	I	−	−	+	30	83	0.20	1.08	36
	P7	M	I	+	−	+	38	144	−1.90	−0.99	15
	P8	F	VI	+	+	+	39	141	−3.60	−0.48	17.1
	P9	M	II	−	−	+	19	130	−1.30	−0.06	9
	P10	M	II	−	−	+	56	164	0.60	−0.1	28.1
	P11	F	IV	+	+	+	121	165	−5.50	1.54	16
	P12	F	IV	+	+	+	81	118	−3.10	−0.30	33.8
	P13	M	II	−	−	+	65	102	0.50	−0.35	22.1
	P14	F	VI	+	+	+	46	152	−4.90	−0.59	6.7
	P15	F	VI	+	+	+	32	116	−2.01	−0.05	33.3
	P16	F	VI	+	+	+	32	115	−3.40	−0.12	32
	P17	F	I	+	+	+	10	102	−2.70	0.91	8.1
	P18	M	VI	+	+	+	59	151	−4.3	0.30	16.8
	P19	M	II	−	−	+	67	85	0.30	−0.01	26.64
	P20	F	VI	+	+	+	100	108	−5.50	−0.47	15
	P21	F	I	+	−	+	8	68	−1.90	0.06	68
	P22	M	VI	+	+	+	85	98	−3.90	−1.28	3.5
	P23	M	VI	+	+	+	20	69	−1.50	0.35	33
	P24	F	VI	+	+	+	67	134	−4.60	−0.36	21.3
	P25	F	I	+	+	+	44	136	−5.30	−0.74	7.6
	P26	M	I	+	+	+	24	62	−2.80	−1.92	19
	P27	F	I	+	+	+	70	97	−2.30	−0.62	13.1
	P28	M	VI	+	−	+	35	65	−1.90	−0.74	24.8
	P29	M	VI	+	−	+	49	67	−0.70	−0.62	24.5
	P30	F	VI	+	−	+	127	132	−0.10	1.38	6.5
Those who were not receiving ERT at the time of DXA scan	P31	M	III	+	+	−	173	173	−3.20	-1.13	16
	P32	M	IV	+	+	−	125	190	−3.40	1.52	18.1
	P33	M	IV	+	+	+	138	143	−3.90	−0.1	15.2
	P34	M	IV	+	+	+	170	168	−3.60	0.51	21.7
	P35	M	IV	+	−	+	44	81	−1.00	0.88	19
	P36	M	IV	+	−	−	35	62	−2.40	−0.73	30
	P37	M	IV	+	+	−	56	100	−3.80	−3.11	36.1
	P38	F	IV	+	+	+	76	76	−1.80	0.53	12.1
	P39	F	IV	+	+	−	175	174	−5.40	1.31	22
	P40	F	VI	+	+	+		182	−3.00	−0.24	5.6
	P41	M	III	−	−	+	50	108	1.30	1.36	12.2
	P42	M	IV	+	+	−	50	101	−3.10	−0.27	8.5
	P43	M	IV	+	−	+	28	72	−2.60	0.18	17
	P44	F	III	+	−	+	109	144	−1.40	0.16	21.7
	P45	M	III	−	−	+	41	197	−1.70	−0.79	23

M: male; F: female; BMD: bone mineral density; 25(OH)D₃: 25 hydroxyvitamin D; HAZ: height-for-age z-score; * −immobile. + mobile
at the time of DXA scan