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Bone mineral density in mucopolysaccharidosis IVB

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ABSTRACT

To date, the only published reports of bone mineral density (BMD) in MPS IV involve patients with MPS IVA; no reports exist describing BMD for MPS IVB. In this prospective study of BMD in three patients with MPS IVB, BMD was acquired by dual-energy X-ray absorptiometry (DXA) at whole body (WB), lumbar spine (LS), and lateral distal femur (LDF). Functional abilities, ambulatory status, medical history, and height z-score were evaluated. Three patients with MPS IVB (two females), aged 17.7, 31.4 and 31.7 years, were evaluated. Every patient was ambulatory and one sustained two fractures caused by trauma. Whole body and hip DXA scans were technically invalid in every patient due to the presence of prosthetic hip hardware. Lumbar spine was valid in only 1 patient due skeletal abnormalities, and was normal (Z-score of −0.8). The LDF was valid in every patient and was low at all three regions of interest: average LDF z-scores were −3.1 (range, −2.9 to −3.6), −2.3 (range, −2.0 to −2.5), and −2.1 (range, −2.0 to −2.3) for region 1–region 3, respectively. Patients with MPS IVB have low BMD of the lower extremities even with full-time ambulation. Routine body sites to measure by DXA were problematic; hip and WB were invalid due to artifact, and LS had limited utility. The LDF was the only body site consistently available on all patients. Patients did not experience low-energy fractures despite low BMD.

1. Introduction

Mucopolysaccharidosis IVB (MPS IVB, Morquio syndrome type B) (OMIM#253010) is an autosomal recessive inherited metabolic disorder caused by deficiency of β-galactosidase (GLB1) [1]. This hydrolase is responsible for the catabolism of terminal β-galactose residues as keratan sulfate (KS) and GM1 ganglioside [2,3]. Keratan sulfate accumulation in patients with MPS IVB causes skeletal dysplasia, growth retardation, keratansulfaturia, corneal clouding, and impaired cardiac function [2,4]. The incidence of MPS IV is variable among different populations (1 per 75,000 in Northern Ireland to 1 per 640,000 in Western Australia) [5,6]. To date more than 180 mutations have been described on *GLB1* (HGMD) [7], but fewer mutations are associated with the clinical phenotype of MPS IVB [2,4,8,9]. There is no cure or established treatment for MPS IVB.

Bone and cartilage are the main tissues affected in patients with MPS IVB, resulting in skeletal dysplasia. However, skeletal and cartilage involvement are not only caused by the primary GAG accumulation but also by disruption of several secondary mechanisms and pathways as: signaling transduction pathways, regulation of humoral factors (chemokines and cytokines), endocytosis, authophagy, apoptosis, oxidative stress, innate and adaptive immune responses [10].

The growth deficits and bone deformities seen in MPS IVB are less severe than those observed in MPS IVA, resulting in a milder phenotype with greater functional abilities. Lack of ambulation is known to negatively impact BMD of the lateral distal femur (LDF) in patients with other medical conditions including cerebral palsy, Duchenne muscular dystrophy, and spina bifida [11–15]. A strong association was demonstrated between low BMD at the LDF and fracture history in children with cerebral palsy and Duchenne muscular dystrophy [16]. Several reports have demonstrated low BMD in MPS IVA [17–20]. One of those reports [17] employed a height adjustment methodology to the DXA results, the HAZ method described by Zemel [21]. The appropriateness of using the HAZ method for children with skeletal dysplasia and who have severe height deficits is questionable [20,22]. Kecskemethy and colleagues reported low BMD of the lower extremities (LDF DXA) in patients with MPS IVA, indicating that the LDF, due to the presence of metallic hardware, intolerance of required position for scan acquisition,

Abbreviations: BMD, bone mineral density; DXA, dual energy X-ray absorptiometry; GAGs, glycosaminoglycans; GLB1, betagalactosidease; HAZ, height-adjusted Z-score; HGMD, The Human Gene Mutation Database; KS, keratan sulfate; LDF, lateral distal femur; LS, lumbar spine; MPS IVB, mucopolysaccharidosis type IV B; NHANES, National Health and Nutrition Survey; WB, whole body.

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and spine abnormalities, is the most accurate and feasible site to measure BMD in MPS IVA [20].

To date, no reports exist describing BMD for MPS IVB; this is the first report of BMD in MPS IVB. We describe BMD measured by DXA at standard body sites and the LDF [23,24], and examine clinical correlates (anthropometric measures, medical and fracture history, and ambulation). Investigation of bone mineral density (BMD) in patients with MPS IVB contributes to understanding of disease pathology.

2. Methods

2.1. Subjects

This cross-sectional study prospectively evaluated three patients with MPS IVB (two females) ranging in age from 17.7 to 31.7 years (mean age 26.9 years) who were enrolled in this study at the Nemours/Alfred I. duPont Hospital for Children (AIDHC). Patients were diagnosed biochemically by enzyme assay. Functional abilities, medical history, tanner score, and height Z-score were reviewed. Radiographs of the lateral spine were used to aid in correct region of interest placement on the lumbar spine (LS) DXA. Age and gender-matched norms were used to calculate Z-scores. Height and weight measures were obtained and height Z-scores were calculated using National Health and Nutrition Survey (NHANES) LMS tables (CDC 2000, accessed 9/5/15) [25]. The maximum age available (19.9 years) was used for patients over this age. Informed consent was applied and the study was approved by the Institutional Review Board of the Institution (338578).

2.2. BMD assessments

Bone mineral density was assessed by DXA at the whole body (WB), lumbar spine LS, and LDF using a Hologic Discovery A model bone densitometer (Hologic, Bedford, MA, USA) located in the AIDHC Medical Imaging Department. All scans were acquired and analyzed by the same DXA technologist. The DXA Z-scores were calculated based on age and gender-matched manufacturer-provided norms and published normative values for the LDF [21]. The oldest normative LDF values available (18 years) were used for the two patients older than 18 years.

The LDF scans were analyzed for three distinct regions of interest, described by Henderson et al., to assess bone density in different types of bone [24]. Region 1 (R1), the most distal region, is predominantly trabecular bone; region 2 (R2) is a mix of trabecular and cortical bone; and region 3 (R3), the most proximal region, is primarily cortical bone (Fig. 1). The LDF BMD was assessed bilaterally, left and right femur BMD values were averaged, and Z-scores were calculated. Abnormal DXA results were defined as more than two standard deviations (SD) below the normal mean, expressed as Z-score < -2 [26]. Radiographs of the LS, including inter-vertebral assessment by DXA, were reviewed by a radiologist and were used to aid in correct region of interest placement on the LS DXA.

3. Results

Three Caucasian patients (two females) with MPS IVB were evaluated; aged 17.7, 31.4 and 31.7 years. Mean height was 131.2 cm (average Z-score −5.4), and mean weight was 39.9 kg (average Z-score −4.0) (Table 1). All patients were ambulatory: two walked independently without any aids and one used a walker and occasionally (once per month) used a wheelchair. One patient sustained two fractures (arm and femur) due to trauma (fall and motor vehicle accident, respectively). All three subjects were post-pubescent.

The presence of metallic artifact from prosthetic hips on every WB scan precluded valid assessment of the results (Fig.2). Metal is interpreted as bone on DXA and therefore the presence of metal artificially elevates BMD. Two of the three patients had vertebral overlap at T12 and L1, invalidating LS scan results. The one technically valid LS scan resulted in a normal BMD Z-score of −0.8, but wedging of L3, which can elevate LS BMD DXA results, was noted [27] (Fig. 3). The LDF yielded technically valid results for all patients, and Z-scores were low at all three regions of interest with average Z-scores of −3.1, −2.3, and −2.1 at R1–R3, respectively (Fig. 4). Every region of interest for all measurements (both femurs) was consistently below normal.

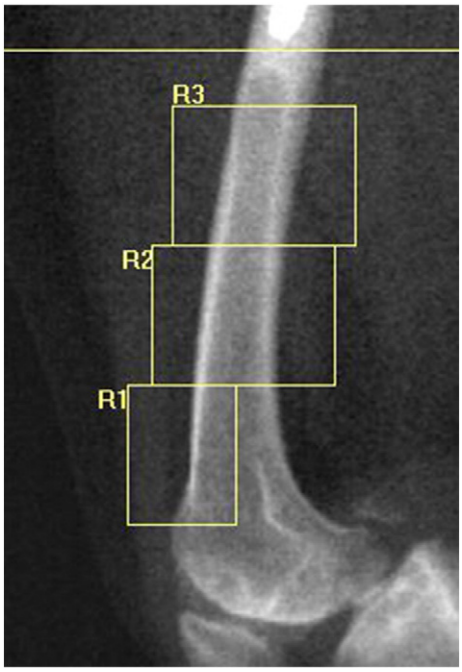

Fig. 1. The LDF DXA scan is analyzed for three regions of interest: Region 1 (anterior distal metaphysis) is essentially trabecular bone, region 2 (metadiaphysis) is composed of both trabecular and cortical bone, region 3 (diaphysis) is composed primarily of cortical bone. There has been proximal femoral surgery with the distal end of the metal prosthesis visible above region 3. LDF DXA, lateral distal femur dual-energy X-ray absorptiometry; R1, region 1; R2, region 2; R3, region 3.

4. Discussion

In this study, we evaluated and reported the BMD of three patients with MPS IVB. The skeletal abnormalities seen in patients with MPS IVB are primarily caused by the accumulation of KS. The exact mechanism of low BMD in MPS IVB is still unknown, although as undegraded substrate accumulates, normal bone and cartilage formation is disrupted leading to impaired homeostasis which could affect BMD [10,28]. Low BMD has also been reported in other lysosomal disorders [28] (e.g. Gaucher's) and skeletal dysplasias [29] (e.g. achondroplasia and hypochondroplasia).

In general, patients with MPS IVB exhibit a less severe phenotype than those with MPS IVA. This fact is evidenced by greater functional ability (all patients were ambulatory) and less severe growth deficits in height resulting in an average height Z-score of −5.4, compared with a group of patients with MPS IVA where nine of 18 patients were fully ambulatory and had an average height Z-score of −7.4 [20].

Ambulation is preservative of bone density as demonstrated by studies examining DXA of the lower extremities in patients with cerebral palsy, Duchenne muscular dystrophy, and spina bifida [11–16]. Henderson et al. described a strong association between fracture and LDF BMD in children with Duchenne muscular dystrophy and cerebral palsy [16]. All of our patients were essentially full-time ambulators (one used a walker and a wheelchair once per month). Despite this ambulation, the LDF BMD was uniformly below normal in all three patients. There was no history of non-traumatic fracture, often seen in patients with low BMD of the lower extremities. It is impossible to examine