HHS Public Access

Author manuscript

J Pediatr Rehabil Med. Author manuscript; available in PMC 2015 May 05.

Published in final edited form as:

J Pediatr Rehabil Med. 2014 ; 7(2): 159–165. doi:10.3233/PRM-140285.

Biomarkers of Bone Remodeling in Children with Mucopolysaccharidosis Types I, II, and VI

David A. Stevenson, MD[1], **Kyle Rudser, PhD**[2], **Alicia Kunin-Batson, PhD**[3], **Ellen B. Fung, PhD, RD**[4], **David Viskochil, MD, PhD**[1], **Elsa Shapiro, PhD**[3], **Paul J. Orchard, MD**[3], **Chester B. Whitley, MD, PhD**[3], and **Lynda E. Polgreen, MD, MS**[3]

[1]University of Utah, Division of Medical Genetics, Department of Pediatrics, Salt Lake City, UT

[2]University of Minnesota, Division of Biostatistics, Minneapolis, MN

[3]University of Minnesota, Department of Pediatrics, Minneapolis, MN

[4]Children's Hospital and Research Center at Oakland, CA

Abstract

Purpose—Skeletal disease causes significant morbidity in mucopolysaccharidoses (MPS), and bone remodeling processes in MPS have not been well characterized. The objective of this study was to determine if biomarkers of bone turnover are abnormal in children with specific MPS disorders (i.e. MSP-I, MPS-II, and MPS-VI) compared to healthy children.

Methods—A cross-sectional study was performed of serum biomarkers of bone formation (bone-specific alkaline phosphatase [BSAP], osteocalcin) and urine biomarkers of bone resorption (pyridinoline, deoxypyridinoline) in MPS and healthy controls. Measures of physical function and pain were obtained using the Children's Health Questionnaire (CHQ).

Results—The cohort consisted of 39 children with MPS (MPS-I=26; MPS-II=11; MPS-VI=4) and 51 healthy children. Adjusting for sex and Tanner stage group, MPS individuals had statistically significant increases for osteocalcin ($p<0.001$), with trends toward higher BSAP ($p=0.054$) and urinary pyridinoline ($p=0.084$). These biomarkers were not significantly associated with CHQ bodily pain and physical-function scores.

Conclusion—Osteocalcin was increased in children with MPS disorders, with trends for increases in BSAP and urinary pyridinoline, suggesting that bone remodeling is altered in children with MPS. Future studies to assess the ability of these biomarkers to quantify and monitor MPS skeletal disease in response to therapy are needed.

Keywords

bone; lysosomal storage diseases; mucopolysaccharidosis; dysostosis multiplex

Corresponding author: David A. Stevenson, MD, University of Utah, Division of Medical Genetics, 2C412 SOM, SLC, UT 84132, Tel: (801) 581-8943, Fax: (801) 585-7252, david.stevenson@hsc.utah.edu.

1. Introduction

The mucopolysaccharidoses (MPS) are a group of lysosomal storage disorders resulting in an accumulation of complex sugars, leading progressive multi-organ system manifestations including skeletal disease [1,2]. The accumulation of glycosaminoglycans (GAG) in MPS disorders can lead to joint contractures, abnormal gait, atlantoaxial instability, short stature, and dysostosis multiplex [3-5]. Dysostosis multiplex in the context of MPS is hypothesized to be associated with abnormalities in bone remodeling given its progressive nature [3]. There are reports of occasional fractures and osteopenia in individuals with MPS [6-9], but their etiologies are not well elucidated and may be secondary to disuse, immobility, abnormal biomechanical forces, inflammatory effects, cell autonomous effects, or some combination of these [2,10].

The skeleton is affected in multiple MPS disorders (e.g. MPS I, II, III, IV, VI, VII, IX) [11]. In particular, MPS I, II, and VI have quite similar skeletal phenotypes and these 3 conditions were the focus of this study. MPS-I is an autosomal recessive disorder due to alpha-L iduronidase deficiency, and the phenotype is characterized based on severity (i.e. Hurler syndrome as the more severe form [MPS-IH], and Hurler-Scheie and Scheie syndromes as the attenutated forms [MPS-IA]). MPS-II (Hunter syndrome) is an X-linked disorder due to iduronate sulfatase deficiency. MPS-VI (Maroteaux-Lamy syndrome) is an autosomal recessive condition due to arylsulfatase B deficiency. Although therapies are available for many MPS disorders, notably enzyme replacement therapy (ERT) and hematopoietic cell transplantation (HCT) [12-20], their beneficial effect on the skeleton is thought to be limited if not initiated early [21]. As new therapies become available, development of biomarkers that are associated with the skeletal manifestations in MPS disorders would be helpful for clinical trials.

The MPS animal models suggest that bone remodeling could be impaired, but the data are limited and conflicting. It has been hypothesized that GAG accumulation impairs bone cellular function, as GAG accumulation has been described in bone cells (e.g. osteoblasts, osteoclasts and chondrocytes) in some MPS animal models [22-25] and in a human case report [26]. Findings from the MPS I mouse model [27] suggest that osteoclast function is impaired, and other MPS animal models show that osteoclasts don’t adhere properly to bone [22].

In more common metabolic disorders of bone such as osteoporosis, biomarkers of bone turnover can help predict long-term disease severity such as fracture risk. The hypothesis is that biomarkers of bone turnover will prove helpful in predicting disease severity and in monitoring therapies for musculoskeletal complications in MPS disorders. The objective of this study wasto determine if biomarkers of bone turnover were abnormal in children with MPS I, II and VI compared to healthy children. The secondary aim was to determine if biomarkers of bone turnover were associated with physical functioning, pain, and height.

2. Methods

Individuals with MPS-IH, MPS-IA, II or VI (ages 5-17.9 years of age) were recruited from treating physicians from multiple centers, the MPS Society Newsletters, website and annual family meeting, and clinicaltrials.gov. The controls were previously recruited from the local community for a separate study of bone and energy metabolism (data unpublished). Informed consent was obtained from the parents or guardians of all participants and assent was obtained from all participants whenever cognitively possible (generally age 7 years or older). The protocol was approved by the Institutional Review Boards at the University of Minnesota and the National Institute of Neurological Disorders and Stroke.

Anthropometric measurements included height measured by wall mounted stadiometer (without shoes) to the nearest 0.1 cm and weight by electronic scale to the nearest 0.1 kg. Age and sex specific standard deviation scores (SDS) were calculated for weight and height using the SAS program from the Centers for Disease Control [http://www.cdc.gov/nccdphp/dnpao/growthcharts/resources/sas.htm, accessed Dec 2012]. Pubertal Tanner stage [28] was assessed by physical examination by a trained study physician. Three groups were identified based on Tanner stage (i.e. Tanner stage 1; Tanner stage 2 and 3; Tanner stage 4 and 5).

Biomarkers were obtained in the morning after fasting for 8 or more hours. Urine was obtained from a single void (first or second morning void). Markers of bone formation measured were serum bone-specific alkaline phosphatase (BSAP) and osteocalcin. Markers of bone resorption were urine pyridinoline (PYD) and deoxypyridinoline (DPD). Urinary DPD was measured using the MicroVue DPD EIA kit, urinary PYD was measured using the MicroVue PYD EIA kit, creatinine was measured using the MicroVue Creatinine EIA kit, and BSAP was measured in serum using the MicroVue BSAP EIA kit all from Quidel Corporation (San Diego, CA). Osteocalcin was measured in plasma using the Human Bone Panel from Millipore Corporation (Billerica, MA). In addition, serum 25-hydroxy vitamin D (25(OH)D) concentrations were also obtained and analyzed by liquid chromatography tandem mass spectroscopy at Fairview Diagnostics Laboratory, Minneapolis, MN.

Measures of physical function and pain were obtained using the Children's Health Questionnaire – Parent form 50 (CHQ-PF50). The CHQ-PF50 is a 50-item, parent-completed questionnaire designed to measure the physical and psychosocial well-being of children between the ages of 5 and 18. The CHQ-PF50 has established reliability and validity and has been widely used in studies of chronic illness in childhood [29-31]. Items are measured on a Likert scale, summed for each subscale and linearly transformed to a 0 to 100 scale, where higher scores reflect better functioning. In this study, CHQ data were obtained only from individuals with MPS disorders.

Descriptive statistics were tabulated separately for the healthy control and MPS groups, which included the mean and standard deviation for continuous variables and frequency for categorical variables. Additive comparisons between group means were adjusted for sex and Tanner stage groups defined above and based on linear regression and the t-distribution with corresponding model degrees of freedom for confidence intervals and p-values. Multiplicative comparisons between group mean formation/resorption ratios used a log link

with a poisson working variance and robust variance estimation for confidence intervals and P-values. Each biomarker and biomarker formation/resorption ratio was evaluated separately. Similarly, the association between differences in biomarker values and outcomes was based on linear regression and the t-distribution for inference. Reported degrees of freedom and test statistics follow the APA formatting style. All analyses were conducted using R v2.15.2 [32].

3. Results

3.1 Participant Demographics/Treatments

Thirty-nine individuals with MPS were included (MPS-IH=19, MPS-IA=5, MPS-II=11 and MPS-VI=4) and compared to 51 controls (Table 1). Controls were, on average, about 2 years older than MPS individuals. All individuals with MPS had previously undergone HCT and/or were receiving ERT. Some individuals who had HCT received ERT before HCT but did not continue after. All children with MPS-IH were treated with HCT at <3 years of age. All children with MPS-IA or MPS-II were being treated with ERT. Two participants with MPS-VI were treated with HCT at ages 1.8 and 3.9 years; the other 2 participants with MPS-VI were being treated with ERT. Twelve participants with MPS were receiving treatment with human growth hormone (hGH) (5 with growth hormone deficiency) for an average of 3.2±2.5 years (range 0.3-8.5 years) and 8 with levothyroxine for hypothyroidism (all with normal free thyroxine and thyroid stimulating hormone levels at the time of the study). Four females and one male had untreated gonadal failure. Individuals with MPS had lower mean 25(OH)D concentrations compared to controls (Table I; $t(78)=6.7$, $p<0.001$). Four of the participants (10%) with MPS had vitamin D deficiency defined as a 25(OH)D concentration <20 ng/ml, which was a significantly higher percentage of subjects compared to controls (0%; $p=0.028$; Fisher's exact test). No individual with MPS or healthy control had a fracture within the year prior to enrollment.

3.2 Bone Biomarkers

Unadjusted mean values for all biomarkers of bone remodeling were higher in the individuals with MPS compared to controls (Table I). Using linear regression to evaluate the difference in biomarkers between MPS versus controls after adjusting for covariates of sex and Tanner stage group separately for each bone biomarker, only osteocalcin remained significantly higher in MPS ($t(85)=3.9$, $p<0.001$; Table II). There were trends for both BSAP ($t(84)=1.95$, $p=0.054$) and urinary PYD ($t(81)=1.75$, $p=0.084$). Noteworthy is that results for urinary DPD and PYD were heavily influenced by one MPS individual with extremely elevated concentrations. When this individual was excluded, differences in DPD and PYD were much more attenuated: difference from control (95% CI) [DPD: −7.8 (−20.4, 4.8), $t(80)=-1.23$, $p=0.221$; PYD: 18.4 (−49.7, 86.5), $t(80)=0.54$, $p=0.592$].

As noted above, the control group was older, with no individuals < 8.5 years of age. When MPS individuals <8.5 years of age (presumably pre-pubertal) were excluded from the analysis (N=10), results were similar in magnitude and strength of association (data not shown).

Multiplicative comparisons of biomarker formation/resorption ratios between MPS versus control groups showed increases for BSAP/DPD, BSAP/PYD, OCN/DPD, and OCN/PYD ratios, although only statistically significant for BSAP/PYD and OCN/PYD ratios (see Table II).

Due to the presence of donor, non-MPS affected osteoclasts in individuals treated with HCT, we divided the MPS group by HCT versus non-HCT for further analysis. When comparing HCT and non-HCT MPS groups to controls, osteocalcin remained significantly higher in both groups ($t(84)=3.95$, $p<0.001$and $t(84)=2.43$, $p=0.017$, respectively). BSAP was also estimated to be higher for both groups compared to controls, but still did not reach statistical significance ($t(83)=1.34$, $p=0.184$ and $t(83)=1.91$, $p=0.060$, respectively). DPD and PYD were significantly higher in the HCT group ($t(80)=2.07$, $p=0.041$and $t(80)=3.55$, $p<0.001$, respectively), and lower on average in the non-HCT group, but not statistically significant ($t(80)=-1.73$, $p=0.087$and $t(80)=-0.79$, $p=0.434$, respectively). Multiplicative comparisons of biomarker formation/resorption ratios between MPS group by HCT and non-HCT versus control groups showed increases in the BSAP/DPD, BSAP/PYD, OCN/DPD, and OCN/PYD ratios for both the MPS HCT and non-HCT groups vs. controls, but were only statistically significant for the MPS non-HCT group when compared to controls (data not shown).

3.3 Association of Biomarkers with Functional Measures

Height SDS, CHQ bodily pain and CHQ physical function scores were not significantly associated with biomarkers of bone metabolism in individuals with MPS after adjusting for Tanner stage group and sex (Table III).

4. Discussion

There are significant musculoskeletal abnormalities in the MPS disorders, and in a majority, dysostosis multiplex is a cardinal feature. Biomarkers of bone remodeling have not previously been evaluated in this population. Animal models suggest that bone cellular functions are abnormal in MPS disorders [22-27]. Our data show that a marker of bone formation is different in children with MPS compared to controls, suggesting increased osteoblast activity. The differences of bone markers in MPS compared to controls may in part be due to factors such as activity level, mobility [33], diet, and other co-morbidities. For example, 25(OH)D concentrations were lower in the MPS group and perhaps this is a consequence of less sun exposure or dietary intake that potentially could have impacted the bone remodeling markers.

We found that the most significant difference in bone biomarker levels was for a marker of bone formation. This may be related to the greater specificity of the markers of bone formation versus the markers of bone resorption that we measured, or a greater impact of the disease process on osteoblasts (bone formation) versus osteoclasts (bone resorption). Osteocalcin is predominantly synthesized by osteoblasts, whereas PYD and DPD are found in other tissues besides bone [34,35]. In addition, we found a trend towards higher BSAP and PYD in individuals with MPS; however, no statistically significant difference was observed. DPD, a related urinary marker of bone resorption was not significantly different.

The reason for this may be because PYD originates from both bone and articular cartilage versus DPD which is not present in cartilage [34,35]. Cartilage abnormalities with increased cartilage break down, similar to inflammatory joint disease, have been well described in MPS animal models [36-39], thus the increased PYD may reflect increased cartilage turnover rather than increased bone resorption.

The osteoclasts of MPS individuals who underwent HCT are donor-derived and bone density changes after HCT can be observed [40,41]. When separating MPS individuals with and without HCT, the respective cohorts became small and hence conclusions are difficult. However, results for bone formation markers were relatively unchanged for both groups compared to controls, whereas bone resorption markers (DPD and PYD) became significantly increased in the HCT group consistent with other studies of children and adults treated with HCT [42-44].

The functional significance of our findings is not certain, as we did not see statistically significant associations between markers of bone turnover and our selected health measures (i.e. CHQ bodily pain, CHQ physical function, and height SDS). As lysosomal storage disorders are rare diseases, our cohort was small which limited our power to detect such associations. Additionally, parent report measures of children's pain and physical functioning may be too distal to be directly associated with biomarkers of bone turnover.

Another limitation is the lack of younger individuals in the control group; however, we obtained similar results when the two groups had similar age distributions by excluding individuals with MPS under age 8.5 years. Also, activity levels likely impact bone turnover and our findings of increased bone biomarkers may be secondary to reduced physical activity and decreased mobility [32], which were not directly measured in the current study. It is also important to note that the MPS group was heterogeneous, consisting of several MPS types and the various treatments (i.e. HCT, ERT), which may have impacted our ability to see associations between bone turnover markers and specific health outcomes.

Despite the limitations, this study represents a relatively large cohort of MPS individuals. The skeletal abnormalities in the MPS disorders can be debilitating and identification of surrogate markers of skeletal disease in MPS will be beneficial in avoiding radiation and high costs of radiographic procedures in monitoring the disease and responses to therapy. It is likely that modifications of current therapies and the addition of new therapies will continue for MPS disorders, and markers of bone metabolism may ultimately be helpful in determining early efficacy and monitoring disease progression of the musculoskeletal manifestations with the various therapies. Future studies with larger cohorts of children with MPS disorders are needed to better understand the potential relationship between biomarkers of bone health and children's physical function, and should include direct measures (e.g. range of motion and six-minute walk tests) and measurements of children's physical activity in daily life (e.g. accelerometry) to better understand the functional significance of these biomarkers for children's quality of life.

5. Conclusion

Osteocalcin was increased in children with MPS disorders, with trends for increases in BSAP and urinary PYD. This study provides evidence that bone biomarkers can potentially be used to quantify and monitor skeletal disease in MPS disorders as additional treatments (e.g., post-HCT supplemental ERT, stop codon suppression drugs, gene therapy, anti-inflammatory therapy) become available for evaluation.

Acknowledgements

This project was supported by Grant Number K23AR057789 from the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), U54NS065768 from the National Institute of Neurological Disorders and Stroke (NINDS), and by Grant Number UL1TR000114-02 from the National Center for Advancing Translational Sciences (NCATS) of the National Institutes of Health (NIH) to the University of Minnesota Clinical and Translational Science Institute (CTSI). Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the CTSI or the NIH.

Disclosure summary: LEP and PO receive grant support from Genzyme. DV receives grant support from Shire. DAS receives honorariums from Guidepoint Global. CBW receives grant support from Genzyme, BioMarin, and Shire.

References

[1]. Vitner EB, Platt FM, Futerman AH. Common and uncommon pathogenic cascades in lysosomal storage diseases. J Biol Chem. 2010; 285:20423–7. [PubMed: 20430897]

[2]. Aldenhoven M, Sakkers RJ, Boelens J, de Koning TJ, Wulffraat NM. Musculoskeletal manifestations of lysosomal storage disorders. Ann Rheum Dis. 2009; 68:1659–65. [PubMed: 19822711]

[3]. Wraith JE. The clinical presentation of lysosomal storage disorders. Acta Neurol Taiwan. 2004; 13:101–6. [PubMed: 15508935]

[4]. Wraith JE. Lysosomal disorders. Semin Neonatol. 2002; 7:75–83. [PubMed: 12069540]

[5]. Valayannopoulos V, Nicely H, Harmatz P, Turbeville S. Mucopolysaccharidosis VI. Orphanet J Rare Dis. 2010; 5:5. [PubMed: 20385007]

[6]. Ransford AO, Crockard HA, Stevens JM, Modaghegh S. Occipito-atlanto-axial fusion in Morquio-Brailsford syndrome. A ten-year experience. J Bone Joint Surg Br. 1996; 78:307–13. [PubMed: 8666648]

[7]. Stevens JM, Kendall BE, Crockard HA, Ransford A. The odontoid process in Morquio-Brailsford's disease. The effects of occipitocervical fusion. J Bone Joint Surg Br. 1991; 73:851–8. [PubMed: 1910048]

[8]. Fung EB, Johnson JA, Madden J, Kim T, Harmatz P. Bone density assessment in patients with mucopolysaccharidosis: a preliminary report from patients with MPS II and VI. J Pediatr Rehabil Med. 2010; 3:13–23. [PubMed: 20617160]

[9]. Polgreen LE, Thomas W, Fung E, Viskochil D, Stevenson DA, Steinberger J, et al. Low Bone Mineral Content and Challenges in Interpretation of Dual-Energy X-Ray Absorptiometry in Children With Mucopolysaccharidosis Types I, II, and VI. J Clin Densitom. 2013 doi:pii: S1094-6950(13)00041-3. 10.1016/j.jocd.2013.03.004. [Epub ahead of print].

[10]. Pastores GM. Musculoskeletal complications encountered in the lysosomal storage disorders. Best Pract Res Clin Rheumatol. 2008; 22:937–47. [PubMed: 19028373]

[11]. Stevenson DA, Steiner RD. Skeletal abnormalities in lysosomal storage diseases. Pediatr Endocrinol Rev. 2013; 10(Suppl 2):406–16. [PubMed: 23858624]

[12]. Decker C, Yu ZF, Giugliani R, Schwartz IV, Guffon N, Teles EL, et al. Enzyme replacement therapy for mucopolysaccharidosis VI: growth and pubertal development in patients treated with recombinant human N-acetylgalactosamine 4-sulfatase. J Pediatr Rehabil Med. 2010; 3:89–100. [PubMed: 20634905]

[13]. Polgreen LE, Tolar J, Plog M, Himes JH, Orchard PJ, Whitley CB, et al. Growth and endocrine function in patients with Hurler syndrome after hematopoietic stem cell transplantation. Bone Marrow Transplant. 2008; 41:1005–11. [PubMed: 18278070]

[14]. Muenzer J, Wraith JE, Clarke LA. International Consensus Panel on Management and Treatment of Mucopolysaccharidosis I. Pediatrics. 2009; 123:19–29. [PubMed: 19117856]

[15]. Wang RY, Bodamer OA, Watson MS, Wilcox WR. on behalf of the ACMG Work Group on Diagnostic Confirmation of Lysosomal Storage Diseases. Lysosomal storage diseases: diagnostic confirmation and management of presymptomatic individuals. Genetics in Medicine. 2011; 13:457–484. [PubMed: 21502868]

[16]. Muenzer J, Beck M, Eng CM, Escolar ML, Giugliani R, Guffon NH, et al. Multidisciplinary management of Hunter syndrome. Pediatrics. 2009; 124:e1228–39. [PubMed: 19901005]

[17]. White KK, Harmatz P. Orthopedic management of mucopolysaccharide disease. J Pediatr Rehabil Med. 2010; 3:47–56. [PubMed: 21791829]

[18]. Giugliani R, Harmatz P, Wraith JE. Management guidelines for mucopolysaccharidosis VI. Pediatrics. 2007; 120:405–418. [PubMed: 17671068]

[19]. Auclair D, Ketteridge D, Oates S, Hopwood JJ, Byers S. An overview of intra-articular therapy for mucopolysaccharidosis VI. J Pediatr Rehabil Med. 2010; 3:3–6. [PubMed: 21791826]

[20]. Tolar J, Grewal SS, Bjoraker KJ, Whitley CB, Shapiro EG, Charnas L, et al. Combination of enzyme replacement and hematopoietic stem cell transplantation as therapy for Hurler syndrome. Bone Marrow Transplant. 2008; 41:531–5. [PubMed: 18037941]

[21]. Malm G, Gustafsson B, Berglund G, Lindström M, Naess K, Borgström B, et al. Outcome in six children with mucoploysaccharidosis type IH, Hurler syndrome, after haematopoietic stem cell transplantation (HSCT). Acta Paediatr. 2008; 97:1108–12. [PubMed: 18452566]

[22]. Monroy MA, Ross FP, Teitelbaum SL, Sands MS. Abnormal osteoclast morphology and bone remodeling in a murine model of a lysosomal storage disease. Bone. 2002; 30:352–9. [PubMed: 11856642]

[23]. Rimoin DL, Silberberg R, Hollister DW. Chondro-osseous pathology in the chondrodystrophies. Clin Orthop Relat Res. 1976; 114:137–152. [PubMed: 816585]

[24]. Nuttall JD, Brumfield LK, Fazzalari NL, Hopwood JJ, Byers S. Histomorphometric analysis of the tibial growth plate in a feline model of mucopolysaccharidosis type VI. Calcif Tissue Int. 1999; 65:47–52. [PubMed: 10369733]

[25]. Russell C, Hendson G, Jevon G, Matlock T, Yu J, Aklujkar M, et al. Murine MPS I: insights into the pathogenesis of Hurler syndrome. Clin Genet. 1998; 53:349–361. [PubMed: 9660052]

[26]. Silveri CP, Kaplan FS, Fallon MD, Bayever E, August CS. Hurler syndrome with special reference to histologic abnormalities of the growth plate. Clin Orthop Relat Res. 1991; 269:305–311. [PubMed: 1907534]

[27]. Wilson S, Hashamiyan S, Clarke L, Saftig P, Mort J, Dejica VM, et al. Glycosaminoglycan-mediated loss of cathepsin K collagenolytic activity in MPS I contributes to osteoclast and growth plate abnormalities. Am J Pathol. 2009; 175:2053–62. [PubMed: 19834056]

[28]. Tanner, JM. Assessment of skeletal maturity and prediction of adult height (TW2 method). Academic Press; London; New York: 1975.

[29]. Apaz MT, Saad-Magalhães C, Pistorio A, Ravelli A, de Oliveira Sato J, Marcantoni MB, et al. Health-related quality of life of patients with juvenile dermatomyostitis: results from the Pediatric Rheumatology International Trials Organisation multinational quality of life cohort study. Arthritis Rheum. 2009; 61:509–17. [PubMed: 19333974]

[30]. Wrotniak BH, Schall JI, Brault ME, Balmer DF, Stallings VA. Health-Related Quality of Life in Children With Sickle Cell Disease Using the Child Health Questionnaire. J Pediatr Health Care. Nov 7.2012 Doi:pii: S0891-5245(12)00190-3. 10.1016/j.pedhc.2012.09.004. [Epub ahead of print].

[31]. Sandstedt E, Fasth A, Eek MN, Beckung E. Muscle strength, physical fitness and well-being in children and adolescents with juvenile idiopathic arthritis and the effect of an exercise programme: a randomized controlled trial. Pediatr Rheumatol Online J. 2013; 11:7. [PubMed: 23432796]

[32]. R Core Team. R: A language and environment for statistical computing. R Foundation for Statistical Computing; Vienna, Austria: 2012. ISBN 3-900051-07-0, URL http://www.R-project.org/

[33]. Guarany NR, Schwartz IV, Guarany FC, Giugliani R. Functional capacity evaluation of patients with mucopolysaccharidosis. J Pedatr Rehabil Med. 2012; 5:37–46.

[34]. Civitelli R, Armamento-Villareal R, Napoli N. Bone turnover markers: understanding their value in clinical trials and clinical practice. Osteoporos Int. 2009; 20:843–51. [PubMed: 19190842]

[35]. Szulc P, Seeman E, Delmas PD. Biochemical measurements of bone turnover in children and adolescents. Osteoporos Int. 2000; 11:281–94. [PubMed: 10928217]

[36]. Eliyahu E, Wolfson T, Ge Y, Jepsen KJ, Schuchman EH, Simonaro CM. Anti-TNF-alpha therapy enhances the effects of enzyme replacement therapy in rats with mucopolysaccharidosis type VI. PLoS One. 2011; 6:e22447. [PubMed: 21887218]

[37]. Simonaro CM, Ge Y, Eliyahu E, He X, Jepsen KJ, Schuchman EH. Involvement of the Toll-like receptor 4 pathway and use of TNF-alpha antagonists for treatment of the mucopolysaccharidoses. Proc Natl Acad Sci U S A. 2010; 107:222–7. [PubMed: 20018674]

[38]. Simonaro CM, D'Angelo M, Haskins ME, Schuchman EH. Joint and bone disease in mucopolysaccharidoses VI and VII: identification of new therapeutic targets and biomarkers using animal models. Pediatr Res. 2005; 57:701–7. [PubMed: 15746260]

[39]. Simonaro CM, Haskins ME, Schuchman EH. Articular chondrocytes from animals with a dermatan sulfate storage disease undergo a high rate of apoptosis and release nitric oxide and inflammatory cytokines: a possible mechanism underlying degenerative joint disease in the mucopolysaccharidoses. Lab Invest. 2001; 81:1319–28. [PubMed: 11555679]

[40]. Petryk A, Bergemann TL, Polga KM, Ulrich KJ, Raatz SK, Brown DM, et al. Prospective study of changes in bone mineral density and turnover in children after hematopoietic cell transplantation. J Clin Endocrinol Metab. 2006; 91:899–905. [PubMed: 16352681]

[41]. Daniels MW, Wilson DM, Paguntalan HG, Hoffman AR, Bachrach LK. Bone mineral density in pediatric transplant recipients. Transplantation. 2003; 76:673–8. [PubMed: 12973107]

[42]. Polgreen LE, Rudser K, Deyo M, Smith A, Baker KS, Petryk A. Changes in biomarkers of bone resorption over the first six months after pediatric hematopoietic cell transplantation. Pediatr Transplant. 2012; 16:852–7. [PubMed: 22905997]

[43]. Kang MI, Lee WY, Oh KW, Han JH, Song KH, Cha BY, et al. The short-term changes of bone mineral metabolism following bone marrow transplantation. Bone. 2000; 26:275–9. [PubMed: 10710001]

[44]. Ebeling PR, Thomas DM, Erbas B, Hopper JL, Szer J, Grigg AP. Mechanisms of bone loss following allogeneic and autologous hemopoietic stem cell transplantation. J Bone Miner Res. 1999; 14:342–50. [PubMed: 10027899]

Table 1

Participant characteristics in children with mucopolysaccharidoses and healthy control children

Covariate	Control (N=51)	MPS (N=39)	MPS IH (N=19)	MPS IA (N=5)	MPS II (N=11)	MPS VI (N=4)
Female	27 (52.9%)	12 (30.8%)	10 (52.6%)	1 (20.0%)	0 (0.0%)	1 (25.0%)
Male	24 (47.1%)	27 (69.2%)	9 (47.4%)	4 (80.0%)	11 (100.0%)	3 (75.0%)
HCT	0 (0.0%)	21 (53.8%)	19 (100.0%)	0 (0.0%)	0 (0.0%)	2 (50.0%)
ERT (at time of evaluation)	0 (0.0%)	18 (46.2%)	0 (0.0%)	5 (100.0%)	11 (100.0%)	2 (50.0%)
Tanner: Pubic Hair						
− 1	3 (5.9%)	18 (46.2%)	10 (52.6%)	0 (0.0%)	8 (72.7%)	0 (0.0%)
− 2 or 3	9 (17.6%)	4 (10.3%)	3 (15.8%)	0 (0.0%)	1 (9.1%)	0 (0.0%)
− 4 or 5	39 (76.5%)	17 (43.6%)	6 (31.6%)	5 (100.0%)	2 (18.2%)	4 (100.0%)
Age (years)	14.6 (2.0)	12.2 (4.0)	10.5 (3.9)	16.7 (1.5)	11.6 (2.9)	16.5 (1.6)
Height SDS	0.3 (1.0)	−2.6 (1.8)	−3.1 (1.5)	−1.6 (1.2)	−1.3 (1.3)	−4.9 (1.2)
Weight SDS	1.2 (1.3)	−1.0 (2.0)	−1.4 (1.4)	0.28 (1.4)	0.38 (1.4)	−4.7 (1.6)
25(OH)D (ng/ml)*	48.9 (16.3)[1]	29.8 (9.3)[9]	35.5 (8.2)[4]	20.5 (7.5)[1]	23.4 (4.0)[2]	33.5 (6.4)[2]
25(OH)D < 20ng/ml	0 (0.0%)	4 (10.3%)	0 (0.0%)	2 (40.0%)	2 (18.2%)	0 (0.0%)
Bone Markers*						
- BSAP (U/L)	94.2 (62.6)	150 (69.9)[1]	150 (67.8)[1]	108 (92.3)	184 (54.6)	108 (59.4)
- DPD (nmol/mmol creatinine)	39.8 (27.4)	53.3 (45.0)[4]	77.2 (55.6)[3]	24.1 (21.8)	38.2 (15.8)	29.6 (13.6)[1]
- PYD (nmol/mmol creatinine)	166 (78.2)	275 (294.5)[4]	417 (387.5)[3]	130 (110.1)	172 (63.5)	140 (59.1)[1]
- OCN (ng/ml)	31.9 (11.4)	50.4 (18.6)	52.7 (18.2)	39.0 (21.8)	52.6 (20.7)	47.7 (6.9)
Formation/Resorption Ratio*						
- BSAP/DPD	3.0 (3.1)	4.2 (3.2)[4]	2.9 (2.7)[3]	6.3 (5.5)	5.3 (2.1)	2.9 (0.7)[1]
- BSAP/PYD	0.54 (0.2)	0.86 (0.7)[4]	0.6 (0.56)[3]	1.2 (1.4)	1.1 (0.39)	0.62 (0.21)[1]
- OCN/DPD	1.2 (1.4)	1.5 (0.93)[4]	1.1 (0.97)[3]	2.1 (1.1)	1.5 (0.71)	1.9 (0.76)[1]
- OCN/PYD	0.22 (0.09)	0.29 (0.18)[4]	0.22 (0.16)[3]	0.37 (0.26)	0.33 (0.15)	0.4 (0.16)[1]
CHQ (standard score 0-100)*						
- Physical Functioning	NA	65.6 (29.2)[8]	61.1 (26.8)[5]	32.2 (21.7)	81.5 (21.3)[2]	94.4 (5.6)[1]
- Bodily Pain	NA	59.7 (28.7)[8]	61.4 (28.5)[5]	42.0 (23.9)	56.7 (29.1)[2]	90.0 (17.3)[1]

J Pediatr Rehabil Med. Author manuscript; available in PMC 2015 May 05.

Values presented are mean (SD) or N (%) where indicated. CHQ=Children's Health Questionnaire; MPS=Mucopolysaccharidoses (MPS IH, MPS IA, MPS II, and MPS VI combined); MPS IH=Hurler syndrome; MPS IA=attenuated form (Hurler-Scheie and Scheie syndromes); MPS II=Hunter syndrome; MPS VI=Maroteaux-Lamy syndrome; OCN=osteocalcin; PYD=pyridinoline; DPD=deoxypyridinoline; Tanner=Tanner stage; SDS=standard deviation score; BSAP=bone specific alkaline phosphatase; HCT=hematopoietic cell transplantation; ERT=enzyme replacement therapy; 25(OH)D= 25 hydroxyvitamin D; NA=not applicable; 25(OH)D conversion: 1 ng/ml=2.496 nmol/l.

* superscript denotes the number missing the respective bone marker/lab value/questionnaire (no superscript = no missing data).

Table 2

Bone marker and formation/resorption ratio comparison between MPS versus control groups, adjusted for sex and Tanner group

Biomarker	***N***	***Additive Difference (95% CI)***	***P-value***
BSAP (U/L)	89	27.5 (−0.5, 55.6)	0.054
DPD (nmol/mmol creatinine)	86	3.0 (−13.9, 19.9)	0.721
PYD (nmol/mmol creatinine)	86	87.7 (−12.0, 187.4)	0.084
OCN (ng/ml)	90	12.7 (6.2, 19.1)	<0.001
Formation/Resorption	***N***	***Multiplicative Difference (95% CI)***	***P-value***
BSAP/DPD	86	1.50 (0.98, 2.30)	0.062
BSAP/PYD	86	1.58 (1.08, 2.33)	0.019
OCN/DPD	86	1.40 (0.99, 1.99)	0.057
OCN/PYD	86	1.43 (1.08, 1.89)	0.012

Tanner stage is grouped into three categories of 1, 2 or 3, and 4 or 5.

MPS=Mucopolysaccharidoses; OCN=osteocalcin; PYD=pyridinoline; DPD=deoxypyridinoline; BSAP=bone specific alkaline phosphatase

Table 3

Association of bone markers with differences in CHQ scores and Height SDS among MPS

Outcome	*N*	*Biomarker*	*Difference in Outcome (95% CI)*	*Model R^2*	*P-value*
CHQ: Physical Function	30	BSAP (per 10)	−1.0 (−2.5, 0.6)	0.293	0.227
CHQ: Bodily Pain	30	BSAP (per 10)	−1.1 (−2.9, 0.6)	0.092	0.199
Height SDS	38	BSAP (per 10)	0.1 (0.0, 0.1)	0.286	0.121
CHQ: Physical Function	27	DPD (per 10)	−0.6 (−3.0, 1.8)	0.315	0.623
CHQ: Bodily Pain	27	DPD (per 10)	−0.3 (−3.0, 2.3)	0.048	0.808
Height SDS	35	DPD (per 10)	0.0 (−0.1, 0.2)	0.228	0.672
CHQ: Physical Function	27	PYD (per 100)	−1.0 (−4.5, 2.6)	0.316	0.605
CHQ: Bodily Pain	27	PYD (per 100)	0.0 (−4.0, 3.9)	0.045	0.988
Height SDS	35	PYD (per 100)	0.0 (−0.2, 0.2)	0.223	0.980
CHQ: Physical Function	31	OCN (per 10)	−2.3 (−8.2, 3.6)	0.272	0.449
CHQ: Bodily Pain	31	OCN (per 10)	−0.8 (−7.5, 5.9)	0.032	0.815
Height SDS	39	OCN (per 10)	0.3 (−0.1, 0.6)	0.286	0.114

The estimates are scaled (per 10 or per 100 as indicated) for interpretation depending on units of the marker. Results are adjusted for sex and Tanner stage group. Tanner stage is grouped into three categories of 1, 2 or 3, and 4 or 5.

CHQ= Children's Health Questionnaire; MPS=Mucopolysaccharidoses; OCN=osteocalcin; PYD=pyridinoline; DPD=deoxypyridinoline; Tanner=Tanner stage; SDS=standard deviation score; BSAP= bone specific alkaline phosphatase