ISOKINETIC STRENGTH DIFFERENCES IN PATIENTS WITH MUCOPOLYSACCHARIDOSIS I, II, AND VI

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The aim of this study was to examine muscular strength differences in patients with Mucopolysaccharidosis (MPS) I, II, or VI versus age- and sex-matched healthy controls. Isokinetic knee extension and flexion strength was measured at 90, 120, and 180 degrees/second (d/s) using a dynamometer in 30 subjects with MPS and 42 controls (9-16 years). MPS-IH (neuropathic), MPS-II, and MPS-VI exhibited significant strength decrements when compared to controls. MPS-IA (non-neuropathic) was not significantly different than controls. MPS-IH and MPS-II had significantly lower dominant leg extension average peak torque (DLEAPT) than controls at 90, 120, and 180d/s. MPS-VI had significantly lower DLEAPT than controls at 90 and 120d/s. At 180d/s, MPS-IH DLEAPT was significantly lower than that of MPS-IA. MPS-IA DLEAPT was not significantly different than controls at any angular velocity. Children with MPS-IH, II and VI have decreased skeletal muscle strength compared to children with MPS-IA.

Key Words: Mucopolysaccharidosis, Strength, Isokinetic
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CHAPTER 1. INTRODUCTION
Mucopolysaccharidosis (MPS) disorders are rare genetic multisystem lysosomal storage disorders that are characterized by the inability to degrade a family of complex carbohydrates called glycosaminoglycans (GAGs). All forms of MPS-I are autosomal recessive disorders caused by an insufficiency of the lysosomal enzyme α-L-iduronidase. MPS I can be divided into two groups, the attenuated forms of MPS-I (Hurler-Scheie and Scheie syndromes [MPS-IA]) and the severe form of MPS-I (Hurler syndrome [MPS-IH]). Mucopolysaccharidosis II (Hunter syndrome [MPS II]) is due to an X-linked genetic mutation to the gene encoding for the enzyme iduronate-2-sulfatase. The enzyme N-acetylgalactosamine 4-sulfatase (arylsulfatase B) is deficient in patients with MPS-VI (Maroteaux-Lamy syndrome) (Giugliani et al., 2010; Sohn et al., 2011; Neufeld & Muenzer, 2001).

These enzyme deficiencies result in an accumulation of GAGs in the cells of various body systems, including cartilage, bone, skin, heart valves, and blood vessels (Braunlin, Berry, & Whitley, 2006; Campos & Monaga, 2012; Dumas et al., 2004; Giugliani et al., 2010; Guarany, Schwartz, Guarany, & Giugliani, 2012; Polgreen & Miller, 2010). The accumulation of GAGs in these tissues results in crowding of the nucleus and swelling of the cell, thus damaging the cell and tissues by affecting intracellular targeting pathways, endocytosis, and autophagy, as well as inhibiting other lysosomal enzymes (Clarke, 2012; Oussoren, Brands, Ruijter, der Ploeg, & Reuser, 2011). As a result, the presentation of MPS
includes coarse facial features, short stature, thickened skin, hepatomegaly, splenomegaly, hernias, and excessive body hair growth. Manifestations to the respiratory system include recurrent infections, obstructive airway disease and obstructive sleep apnea. There are also cardiac implications involving cardiac valvular thickening, coronary artery disease, and conduction abnormalities (Braunlin et al., 2011). Finally, MPS results in claw-like hands, progressive joint stiffness, and carpal tunnel syndrome, which can restrict hand and joint mobility and function. (Giugliani et al., 2010; Manger, Mengel, Schaefer, 2007; Morishita & Petty, 2011; Pastores & Meere, 2004; Sohn et al., 2011).

Treatment-based and characterization studies that aim to evaluate the musculoskeletal system in MPS patients often focus solely on skeletal abnormalities (Fung, Johnson, Madden, Kim, & Harmatz, 2010; Oussoren et al., 2011; Weisstein, Delgado, Steinbach, Hart, & Packman, 2004). The few studies that do have a comprehensive musculoskeletal system focus employ functional tests including the 6- or 12-minute walk test, 3-min stair-climb, and/or goniometric tests for joint mobility for evaluation (Cardoso-Santos et al., 2008; Dumas et al., 2004; Guarany et al., 2012; Harmatz et al., 2005; Sohn et al., 2012). To date, little is known about muscular strength decrements due to MPS.

The primary aim of this study was to determine skeletal muscle strength differences in patients with MPS-I, II, or VI versus age- and sex-matched healthy
controls. We hypothesized that all MPS subgroups studied would have decreased strength compared to healthy controls. Based on the severity of the MPS-IH phenotype, it was hypothesized that MPS-IH would have the greatest decrease in skeletal muscle strength (Giugliani et al., 2010; Manger, Mengel, & Schaefer, 2007; Weisstein et al., 2004). It was further hypothesized that MPS-VI and MPS-IA groups would have significantly less strength than controls but more strength than the MPS-IH group as a result of less neurologic involvement (Cardoso-Santos et al., 2008; Giugliani et al., 2010; Sohn et al., 2012). Finally, we hypothesized that MPS-II subjects would have the least skeletal muscle strength decrements compared to the control group due to the X-linked genetic basis of the genotype (Giugliani et al., 2010).

A complete literature review, as well as a subsequent methodology, results, discussion, and conclusion surrounding this study are detailed in the following chapters. Chapter two provides background on the physiological basis of MPS and summarizes the current literature related to symptoms and epidemiology of symptoms of MPS. Treatment-based and characterization studies of the musculoskeletal system of MPS patients will be discussed to expose the absence of a direct measure of muscular strength. Chapter three addresses the methodology of this study, including recruitment of the study population; data abstraction and measurement techniques; as well as statistical analysis. Chapter four details the results of this study by examining the knee
extension and flexion dynamometric variables peak torque, peak torque per unit body weight, average power, and dominant leg extension average peak torque, as well as differences observed between MPS types. Chapter five summarizes and discusses the implications of these findings with reference to the current literature. Limitations of the study are also discussed. Chapter six offers conclusions of the resulting study, and states the necessity for future research into the muscular strength of patients with MPS.
CHAPTER 2. REVIEW OF LITERATURE
Glycosaminoglycans (GAGs) play an important role in the cell-extracellular matrix (ECM) interface. The four subfamilies of GAGs are chondroitin/dermatan sulphate, heparan sulphate/heparin, hyaluronan, and keratin sulphate. They are linear polysaccharides composed of a repeating disaccharide unit of a hexosamine and a hexuronic acid. The monosaccharides are connected through a glycosidic linkage. The synthesis of GAGs takes place in either the GAGosome of the Golgi apparatus or via an integral plasma membrane synthase (Sasisekharan, Raman, & Prabhakar, 2006; Viola, Douglas, Alaniz, & Bartolini, 2012). The negatively charged GAGs are covalently attached to a protein core forming a proteoglycan (Oussoren et al., 2011; Sasisekharan, Raman, & Prabhakar, 2006). The negativity of GAGs attracts osmotically active cations, causing water to diffuse into the ECM (Alberts et al., 2009). The water and repulsive electrostatic forces between negative charges allows for the ECM to resist compression and absorb shocks (Alberts et al., 2009; Oussoren et al., 2011). The depolymerization of GAGs is accomplished by glycosidases and lysosomal sulfatases (Sasisekharan, Raman, & Prabhakar, 2006).

**Mucopolysaccharidoses I, II, and VI**

All forms of MPS-I are autosomal recessive disorders characterized by an insufficiency or lack of activity of α-L-iduronidase (IDUA) enzyme, thereby causing an accumulation of the GAGs dermatan sulfate and heparan sulfate. The prevalence of MPS-IH is 1 in 100,000 births, whereas the prevalence of MPS-IA
is 1 in 800,000 births (Lowry, Applegarth, Toone, MacDonald, Thunem, 1990; Meikle, Hopwood, Clague, & Carey, 1999; Nelson, 1997; Neufeld & Muenzer, 2001; Poorthuis et al., 1999). Joint contractures are also observed in MPS-IH patients. In MPS-IH, the accumulation of GAGs leads to neurocognitive deficits, whereas in MPS-IA there are no neurocognitive deficits (Giugliani et al., 2010).

MPS-II is an X-linked genetic mutation to the gene encoding for the lysosomal enzyme iduronate-2-sulfatase. Due to the X-linked heritance, it is found nearly entirely in males. The prevalence of MPS-II is 0.31 to 0.71 per 100,000 births (Nelson, 1997; Nelson, Crowhrst, Carey, & Greed, 2003). Similarly to the forms of MPS-I, the metabolism of GAGs dermatan sulfate and heparan sulfate is incomplete. Clinical findings are very similar to MPS-I. There is a severe form (neuropathic) and an attenuated form (non-neuropathic) (Martin et al., 2008; Wraith et al., 2008).

The enzyme N-acetylgalactosamine 4-sulfatase is deficient in patients with MPS-VI (Sohn et al., 2011; Neufeld & Muenzer, 2001). The deficiency in this enzyme results in partially degradation of dermatan sulfate, and therefore its accumulation. Somatic involvement can resemble MPS-I; however, MPS-VI patients typically do not have neurocognitive involvement (Giugliani et al, 2010). The skeletal system is highly affected through the progressive course of the disease.
Functional tests as a measure of musculoskeletal system involvement in characterization and treatment-based studies

Early studies examining the functional consequences of musculoskeletal system disease progression in the MPS population involved developing physical performance tests. Dumas et al. (2004) used walk and goniometric tests, as well as arm and leg functional tests (i.e. backpack donning and putting on pants) and endurance tests (3-minute walk test at two speeds) to generate a field-compatible performance measure unique to Mucopolysaccharidosis (MPS-PPM). The study used a convenience sample of 10 MPS-I subjects. Upon completion of each of the 14 performance items, subjects were scored based on their performance and speed of task completion. The study demonstrated that individuals with MPS-I have difficulty in performance of arm and leg function and reduction of functional endurance. With increasing age, subjects demonstrated greater severity in physical performance ($r=0.72$, $p<0.05$), lower leg function ($r=-0.67$, $p<0.05$), and reduced endurance ($r=-0.65$, $p<0.05$). In general, subjects exhibited decreased speed of movement, reductions in shoulder flexion range of motion, reduction in fine motor performance, reduced lower-limb flexibility, diminished walking speed and limited cardiovascular endurance. Researchers noted that reductions in lower extremity flexibility appeared to have the greatest impact on physical functional performance (Dumas et al., 2004).
Haley et al. (2006) sought to decrease the number of tests within the MPS-PPM measure and develop normative scores to provide a reference for age-based comparisons by using a convenience sample of 150 normal, healthy children and adolescents. A retrospective review of the data from the 10 MPS subjects of the Dumas et al. (2004) study was used for comparison. Results of the study clearly demonstrated the severity in which the physical performance of individuals with MPS-I is affected compared to normal, healthy subjects.

Results of treatment-based studies examining the musculoskeletal system in the MPS population have varied. Harmatz et al. (2005) investigated the effectiveness of enzyme replacement therapy (ERT) on 12-minute walk distance, 6-minute walk distance (evaluated at the 6-minute time point of the 12-minute walk test), 3-minute stair climb, and shoulder range of motion in 10 patients with MPS-VI. The duration of the study was 48 weeks. Throughout the duration patients received weekly intravenous treatments of 1.0 mg/kg recombinant human N-acetylgalactosamine 4-sulfatase. On average, patients increased their 12-minute walk distance by 138%, walk distance was improved by 80% at the 6-minute time point of the 12-minute walk test, and a 147% improvement was observed in the 3-minute stair climb. Joint pain and stiffness, as measured by a questionnaire, improved by 50%. However, only small improvements were observed in shoulder range of motion.
Conversely, Guarany and colleagues (2012) studied the effect of ERT on functional capacity and joint range of motion in patients with MPS and observed no positive effect. The study consisted of three groups (1: patients not on ERT during the study, 2: Patients on ERT at the time of study inclusion that remained on ERT, 3: patients who started ERT after study inclusion). Group 1 was composed of three MPS-II, two MPS-IIIB, and two MPS-IVA; group 2 comprised of three MPS-I and three MPS-VI; and group 3 consisted of three MPS-I, four MPS-II, and one MPS-VI. Functional capacity was evaluated via the Pediatric Evaluation of Disability Inventory for subjects below the age of 7 years and 11 months, and the Functional Independence Measure for subjects above 8 years of age. Each of these functional measures has a mobility component. Joint range of motion was assessed at the shoulder, elbow, wrist, hip, knee, and ankle. Compromise of functionality and joint range of motion was observed in MPS-I, II, IIIB, IVB, and VI. The study did not observe a significant effect of ERT on the parameters analyzed.
CHAPTER 3. METHODOLOGY
Experimental subjects

Twenty-six individuals with MPS-IH, IA, II, or VI were recruited from a larger 5-year, observational study of bone and endocrine disease in children with MPS. In addition, forty-two age- and sex-matched, healthy subjects were recruited to serve as controls from a study of childhood cancer survivors, in which they also served as controls (Polgreen et al., 2012). Informed consent was obtained from the parents or legal guardians of all subjects. Assent was obtained from all subjects whenever cognitively possible. All subjects included were between 9 and 16 years of age. Exclusion criteria for the MPS subjects were pregnancy, radiation exposure in the previous 12 months above 500 mrem, non-English speaking, or inability to comply with study procedures. Exclusion criteria for the control subjects were chronic illnesses including hypothyroidism and delayed puberty, or at risk for growth hormone deficiency. The study protocols were approved by the University of Minnesota Institutional Review Board.

Isokinetic strength evaluation

Subjects were seated in the chair of the Biodex dynamometer (Biodex Medical Systems, Inc., Shirley, NY, USA). The chair was adjusted for correct alignment with the knee attachment, hip flexion at 85°, and the axis of the lever arm visually aligned with the knee’s anatomical axis of rotation. Stabilization straps were placed around the waist and around the mid-thigh of the test leg. In subjects who were tall enough, stabilization straps were also placed across the
torso so that the straps did not cross at the level of their neck. The range of motion at the knee, limb weight, and reference position (90° flexion) were determined using the dynamometer.

Bilateral isokinetic knee extension and flexion strength was measured at angular velocities of 90, 120, and 180 degrees per second (d/s). Subjects were instructed to provide a maximal effort. The tests at 90 and 120 d/s involved 6 kicks (extension then flexion is one kick). The participant kicked 20 consecutive times for the 180 d/s test.

Peak torque (PT), peak torque per unit body weight (PT/BW) and average power (AP) were calculated for each leg. The strength measure dominant leg extension average peak torque (DLEAPT) was determined during data entry from the test output of each subject.

**Statistical Analysis**

Statistical analysis was performed using IBM SPSS Statistics 19 software (SPSS, Chicago, IL, USA). Group differences in demographic variables (age, sex, height, weight) and strength variables (PT, PT/BW, AP, DLEAPT) were determined using a Dunnett’s T3 planned comparison. Mean height and weight z-scores relative to age and gender from the Centers for Disease Control and Prevention growth data were calculated (CDC, 2000). The comparison between
controls and the collective MPS group (All MPS) were determined via an independent t-test with equal variances not assumed. An alpha level of 0.05 was used to determine statistical significance.
CHAPTER 4. RESULTS
Characteristics of the patients

Table 1 contains demographic characteristics of the subjects. All participants ranged from 9 to 16 years of age. Due to MPS-II having an X-linked genetic origin, MPS-II had a significantly (p<0.05) larger proportion of males compared to the controls and MPS-IH. Controls were significantly taller and weighed more than MPS-IH and MPS-II. The MPS-IA group was also significantly taller than MPS-IH and MPS-II.

Strength measurements

The MPS-IA group was not significantly different from controls for any strength variable at any angular velocity. For every strength variable at each angular velocity, MPS-IH was significantly weaker than controls, with the exception of right knee flexion at 180 d/s (Figure 1, Table 2 and 3).

Dominant leg extension average peak torque (DLEAPT). MPS-IH and MPS-II were significantly lower than controls at 90d/s (MPS-IH 13.8±1.9, MPS-II 22.3±3.9 vs. control 51.9±3.6 ft-lbs); 120d/s (MPS-IH 14.2±2.1, MPS-II 25.3±5.2, vs. control 48.4±3.4 ft-lbs); and 180d/s (MPS-IH 13.7±1.9, MPS-II 21.5±4.0, vs. control 40.1±2.7 ft-lbs). The MPS-VI group was significantly lower than controls at 90d/s (MPS-VI 25.5±3.9 vs. control 51.9±3.6 ft-lbs) and 120d/s (MPS-VI 24.6±4.2 vs. control 48.4±3.4 ft-lbs). At 180d/s, MPS-IH was significantly lower than MPS-IA (MPS-IH 13.7±1.9 vs. MPS-IA 39.2±5.0 ft-lbs).
Right and left leg peak torque (PT), peak torque per unit body weight (PT/BW) and average power (AP). There were four significant differences observed between the MPS groups. At 90 d/s, MPS-IH had significantly lower PT/BW for right knee extensions than MPS-II (Table 2). The MPS-IH group also had significantly lower PT for right and left knee extension at 180 d/s (Table 2). For left knee flexion, MPS-IH PT at 90 d/s was significantly lower than that of MPS-VI (Table 3).

At each angular velocity, MPS-II had significantly lower PT and AP for right and left knee extension compared to controls (Table 2 and 3). At 90 and 120 d/s, MPS-II also had significantly lower right knee extension PT/BW than controls (Table 2). At 90 and 120 d/s, MPS-II had significantly lower PT and AP for right knee flexion compared to controls (Table 3). Left knee flexion PT and AP at 90 d/s was also significantly lower than controls (Table 3). Peak torque for left knee flexion at 180 d/s was significantly lower in MPS-II compared to controls (Tables 3). When PT was observed to be significantly different than controls, this significance was often lost when normalized per body weight (PT/BW) (Tables 2 and 3).

Compared to controls, MPS-VI had significantly lower PT and AP for right knee extension at 90 and 120 d/s (Table 2). At 180 d/s, MPS-VI was also had significantly lower right knee extension PT compared to controls. During left knee
extension at 90 d/s, MPS-VI had significantly lower PT and AP than controls. For right knee flexion PT and AP, MPS-VI was significantly lower than controls at each angular velocity (Table 3). The MPS-VI group was also significantly lower for left knee flexion PT and AP at 90 d/s compared to controls. Following normalization of PT per body weight (PT/BW), MPS-VI was no longer observed to be significantly different than controls (Tables 2 and 3).
CHAPTER 5. DISCUSSION
The present study observed that skeletal muscle strength differed between MPS groups; with MPS-IH, MPS-II and MPS-VI having significantly lower strength than controls. The MPS-IA group was not significantly different than controls for any strength variable analyzed. The level of attenuation observed in the MPS-IA group was unexpected because individuals with MPS-IA generally have less severe skeletal manifestations than individuals with MPS-IH (de Ru et al., 2012; Morishita & Petty, 2011).

For MPS-II and MPS-VI, the significant differences observed in PT were often lost when PT was normalized for body weight (PT/BW). Greater body mass induces greater loading on the musculature of the lower body, thus stimulating muscle adaption (Capodaglio et al., 2009). Peak torque, an absolute measure, is likely higher in controls due to higher absolute fat-free mass. The loss of significance after normalization for body weight suggests that MPS-II and MPS-VI may have appropriate strength for their body size.

The severity of skeletal abnormalities in the various MPS types has been previously reported (Manger, Mengel, & Schaefer, 2007; Morishita & Petty, 2011; Oussoren et al., 2011; Pastores & Meere, 2004; Weisstein et al., 2004). Joint stiffness and contractures are symptoms of nearly all MPS types (Morishita & Petty, 2011; Oussoren et al., 2011). The symptoms are a result of GAG accumulation in ligaments, tendon, and joint capsules (Morishita & Petty, 2011;
Pastores & Meere, 2004; Weisstein et al., 2004), which results in inflammatory changes (Simonaro, D'Angelo, Haskins, & Schuchman, 2005; Simonaro, Haskins, & Schuchman, 2001). The present study suggests a relationship between muscular strength decrements and degree of skeletal system disease severity as we were able to clearly differentiate between the severe vs. attenuated forms of MPS I.

In some MPS types there is a secondary accumulation of GAGs in the brains of patients. The accumulation of GAGs is thought to contribute to neuropathology affecting synaptic connectivity and plasticity of neurons (Buchino & Vogler, 1998; McGlynn, Dobernis, & Walkley, 2004; Parkinson-Lawrence et al., 2010). Degree of neurological involvement may also play a significant role in the differences observed in DLEAPT, PT, PT/BW, and AP between MPS phenotypes. There can be substantial neurological involvement in MPS-IH and some forms of MPS-II. Dusing et al. (2006) observed below-average gross motor abilities in MPS-IH, which may contribute to MPS-IH subjects’ significant decreased knee flexion and extension strength as measured by a dynamometer. Further research into muscular strength is needed for a more definitive explanation as to the reason for the observed differences in muscular strength in the various MPS phenotypes.

The most significant potential limitation of the present study is the inability
to address the contribution of neurological deficits in the strength decrements demonstrated. Additionally, there is always the concern of effort in any study involving children. Although participants were instructed to provide a maximal effort, no measurements of muscle activation (i.e. electromyography) were made.
CHAPTER 6. CONCLUSION
Unlike children with MPS-IA, children with MPS-IH, II or VI have decreased skeletal muscle strength. Decrements in skeletal muscle strength greatly depend on MPS diagnosis. Isokinetic strength measures have the potential to be used as an objective measure of skeletal muscle strength to quantify the effect of MPS-diagnosis-specific intervention on muscular disease.

Recommendations for further research include using dominant leg extension average peak torque, peak torque, peak torque per unit body weight, and average power to quantify the effect of interventions on muscular disease in MPS. Additionally, pre-treatment strength results in intervention studies can confirm the results presented in this study.


heterogeneity in MPS I: Results of an international consensus procedure. 

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APPENDIX
Definitions of isokinetic strength variables

**Peak torque (PT).** An absolute measure of the highest muscular force output at any moment during a repetition. PT represents the maximum strength ability the exercised muscles (Grabnier, 1997).

**Peak torque/body weight (PT/BW).** A relative measure of the highest muscular force output at any moment during a repetition. Represented as a percent normalized to the body weight of the participant (Grabnier, 1997).

**Average Power (AP).** Amount of total work divided by the time to complete that total work. Average power provides a measure of the work rate intensity and how quickly a muscle can produce force (Grabnier, 1997).

**Dominant Leg Extension Average Peak Torque (DLEAPT).** Average peak torque is the average of the peak torque values generated during a series of repetitions. This measure may be considered a better estimate of overall function than PT, since function is dependent on repetition of movement (Grabnier, 1997). Only average peak torque during extension of the subject’s dominant leg was used for data analysis.
Table 1. Demographics of study population (mean ± standard error or N).

<table>
<thead>
<tr>
<th></th>
<th>Control (N=42)</th>
<th>All MPS (N=30)</th>
<th>MPS IH (N=12)</th>
<th>MPS IA (N=6)</th>
<th>MPS II (N=8)</th>
<th>MPS VI (N=4)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td>12.3 ± 0.3</td>
<td>12.2 ± 0.5</td>
<td>11.1 ± 0.9</td>
<td>14.6 ± 1.0</td>
<td>11.0 ± 0.8</td>
<td>14.5 ± 1.3</td>
</tr>
<tr>
<td><strong>Sex (male/female)</strong></td>
<td>32/10</td>
<td>21/9</td>
<td>5/7</td>
<td>5/1</td>
<td>8/0*†</td>
<td>3/1</td>
</tr>
<tr>
<td><strong>Height (Z-score^)</strong></td>
<td>0.77 ± 0.2</td>
<td>-2.5 ± 0.3*</td>
<td>-3.1 ± 0.5*</td>
<td>-0.87 ± 0.6</td>
<td>-2.0 ± 0.5*</td>
<td>-4.1 ± 0.8*</td>
</tr>
<tr>
<td><strong>Weight (Z-score^)</strong></td>
<td>0.66 ± 0.1</td>
<td>-1.1 ± 0.3*</td>
<td>-1.5 ± 0.6*</td>
<td>-0.36 ± 0.7</td>
<td>-0.43 ± 0.4</td>
<td>-3.2 ± 0.6*</td>
</tr>
</tbody>
</table>

* p<0.05 significantly different than controls; † p<0.05 significantly different than MPS-IA

^ Z-score relative to age and gender from Centers for Disease Control and Prevention growth data

MPS-IH, mucopolysaccharidosis I Hurler syndrome; MPS-IA, mucopolysaccharidosis I attenuated; MPS-II, mucopolysaccharidosis II; MPS-VI, mucopolysaccharidosis VI; N, sample size
Table 2. Mean (± standard error) strength measures of knee extension in study population at 90, 120, and 180 degrees/second (d/s)

<table>
<thead>
<tr>
<th>Angular Velocity</th>
<th>Strength Variable</th>
<th>Control</th>
<th>MPS-IH</th>
<th>MPS-IA</th>
<th>MPS-II</th>
<th>MPS-VI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>90 d/s</strong></td>
<td>Right Knee</td>
<td>PT (FT-LBS)</td>
<td>57.8 ± 4.0</td>
<td>16.4 ± 2.6*</td>
<td>58.2 ± 12.6</td>
<td>30.0 ± 4.4*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PT/BW (%)</td>
<td>52.2 ± 2.1</td>
<td>24.0 ± 2.3*</td>
<td>51.6 ± 10.6</td>
<td>38.7 ± 3.4*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AP (Watts)</td>
<td>66.5 ± 4.7</td>
<td>13.3 ± 2.5*</td>
<td>65.2 ± 16.4</td>
<td>32.2 ± 5.5*</td>
</tr>
<tr>
<td><strong>90 d/s</strong></td>
<td>Left Knee</td>
<td>PT (FT-LBS)</td>
<td>57.6 ± 3.8</td>
<td>17.0 ± 3.0*</td>
<td>58.8 ± 11.9</td>
<td>30.2 ± 5.3*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PT/BW (%)</td>
<td>52.7 ± 2.2</td>
<td>24.6 ± 2.4*</td>
<td>55.6 ± 15.1</td>
<td>38.4 ± 4.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AP (Watts)</td>
<td>66.8 ± 4.6</td>
<td>15.0 ± 3.2*</td>
<td>63.6 ± 16.1</td>
<td>34.0 ± 6.2*</td>
</tr>
<tr>
<td><strong>120 d/s</strong></td>
<td>Right Knee</td>
<td>PT (FT-LBS)</td>
<td>53.9 ± 3.6</td>
<td>16.7 ± 2.7*</td>
<td>53.6 ± 10.3</td>
<td>27.0 ± 4.9*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PT/BW (%)</td>
<td>49.2 ± 2.1</td>
<td>24.4 ± 2.2*</td>
<td>51.5 ± 14.2</td>
<td>34.3 ± 3.5*</td>
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<td></td>
<td></td>
<td>AP (Watts)</td>
<td>80.0 ± 6.0</td>
<td>17.7 ± 3.6*</td>
<td>74.0 ± 16.7</td>
<td>36.7 ± 7.6*</td>
</tr>
<tr>
<td><strong>120 d/s</strong></td>
<td>Left Knee</td>
<td>PT (FT-LBS)</td>
<td>53.2 ± 3.6</td>
<td>16.8 ± 2.6*</td>
<td>54.1 ± 10.7</td>
<td>29.1 ± 4.8*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PT/BW (%)</td>
<td>49.1 ± 2.2</td>
<td>24.7 ± 2.2*</td>
<td>50.8 ± 12.8</td>
<td>37.4 ± 4.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AP (Watts)</td>
<td>79.7 ± 5.6</td>
<td>18.3 ± 3.9*</td>
<td>75.5 ± 18.9</td>
<td>41.7 ± 7.8*</td>
</tr>
<tr>
<td><strong>180 d/s</strong></td>
<td>Right Knee</td>
<td>PT (FT-LBS)</td>
<td>47.2 ± 3.1</td>
<td>17.0 ± 2.5*</td>
<td>47.1 ± 7.1†</td>
<td>26.8 ± 4.8*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PT/BW (%)</td>
<td>43.7 ± 1.9</td>
<td>25.2 ± 2.0*</td>
<td>46.0 ± 12.1</td>
<td>34.0 ± 3.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AP (Watts)</td>
<td>86.3 ± 6.8</td>
<td>21.1 ± 4.1*</td>
<td>74.8 ± 14.75</td>
<td>41.3 ± 9.6*</td>
</tr>
<tr>
<td><strong>180 d/s</strong></td>
<td>Left Knee</td>
<td>PT (FT-LBS)</td>
<td>46.6 ± 3.1</td>
<td>15.9 ± 2.1*</td>
<td>46.4 ± 6.7†</td>
<td>27.5 ± 4.6*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PT/BW (%)</td>
<td>43.2 ± 2.0</td>
<td>23.9 ± 2.0*</td>
<td>48.1 ± 15.5</td>
<td>35.1 ± 3.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AP (Watts)</td>
<td>83.6 ± 6.4</td>
<td>20.2 ± 3.8*</td>
<td>74.7 ± 14.8</td>
<td>45.0 ± 10.0*</td>
</tr>
</tbody>
</table>

*p<0.05 significantly different than controls; †p<0.05 significantly different than MPS-IH
MPS-IH, mucopolysaccharidosis I Hurler syndrome; MPS-IA, mucopolysaccharidosis I attenuated; MPS-II, mucopolysaccharidosis II; MPS-VI, mucopolysaccharidosis VI; PT, peak torque; PT/BW, peak torque per unit body weight; AP, average power
Table 3. Mean (± standard error) strength measures of knee flexion in study population at 90, 120, and 180 degrees/second (d/s)

<table>
<thead>
<tr>
<th>Angular Velocity</th>
<th>Strength Variable</th>
<th>Control</th>
<th>MPS-IH</th>
<th>MPS-IA</th>
<th>MPS-II</th>
<th>MPS-VI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>90 d/s</strong></td>
<td>PT (FT-LBS)</td>
<td>30.3 ± 2.4</td>
<td>9.7 ± 1.6*</td>
<td>32.4 ± 7.7</td>
<td>16.6 ± 2.9*</td>
<td>14.2 ± 3.1*</td>
</tr>
<tr>
<td></td>
<td>PT/BW (%)</td>
<td>27.3 ± 1.4</td>
<td>14.3 ± 1.7*</td>
<td>29.4 ± 7.4</td>
<td>21.6 ± 2.8</td>
<td>19.5 ± 3.8</td>
</tr>
<tr>
<td></td>
<td>AP (Watts)</td>
<td>32.6 ± 3.3</td>
<td>6.3 ± 1.7*</td>
<td>33.4 ± 9.0</td>
<td>17.1 ± 3.4*</td>
<td>12.8 ± 3.5*</td>
</tr>
<tr>
<td><strong>Left Knee</strong></td>
<td>PT (FT-LBS)</td>
<td>30.5 ± 2.2</td>
<td>10.5 ± 1.4*</td>
<td>30.7 ± 17.7</td>
<td>16.1 ± 3.1*</td>
<td>17.5 ± 0.8*†</td>
</tr>
<tr>
<td></td>
<td>PT/BW (%)</td>
<td>27.7 ± 1.3</td>
<td>15.6 ± 1.3*</td>
<td>28.0 ± 7.6</td>
<td>20.4 ± 2.7</td>
<td>25.4 ± 5.1</td>
</tr>
<tr>
<td></td>
<td>AP (Watts)</td>
<td>33.1 ± 3.1</td>
<td>7.5 ± 1.8*</td>
<td>30.4 ± 9.5</td>
<td>15.7 ± 4.1*</td>
<td>15.8 ± 2.1*</td>
</tr>
<tr>
<td><strong>120 d/s</strong></td>
<td>PT (FT-LBS)</td>
<td>29.3 ± 2.6</td>
<td>9.9 ± 1.9*</td>
<td>31.1 ± 6.6</td>
<td>15.8 ± 2.8*</td>
<td>14.3 ± 1.6*</td>
</tr>
<tr>
<td></td>
<td>PT/BW (%)</td>
<td>26.1 ± 1.5</td>
<td>15.2 ± 1.2*</td>
<td>29.9 ± 8.9</td>
<td>20.6 ± 2.9</td>
<td>20.8 ± 4.7</td>
</tr>
<tr>
<td></td>
<td>AP (Watts)</td>
<td>40.7 ± 4.3</td>
<td>8.0 ± 2.5*</td>
<td>43.2 ± 10.4</td>
<td>18.6 ± 4.5*</td>
<td>15.1 ± 2.5*</td>
</tr>
<tr>
<td><strong>Left Knee</strong></td>
<td>PT (FT-LBS)</td>
<td>28.7 ± 2.3</td>
<td>10.4 ± 1.6*</td>
<td>30.9 ± 7.2</td>
<td>17.2 ± 3.4</td>
<td>18.0 ± 2.7</td>
</tr>
<tr>
<td></td>
<td>PT/BW (%)</td>
<td>26.1 ± 1.5</td>
<td>15.2 ± 1.2*</td>
<td>27.3 ± 6.3</td>
<td>22.3 ± 3.7</td>
<td>25.3 ± 4.6</td>
</tr>
<tr>
<td></td>
<td>AP (Watts)</td>
<td>40.7 ± 4.3</td>
<td>8.0 ± 2.5*</td>
<td>37.9 ± 10.8</td>
<td>19.9 ± 5.8</td>
<td>22.4 ± 5.4</td>
</tr>
<tr>
<td><strong>180 d/s</strong></td>
<td>PT (FT-LBS)</td>
<td>27.4 ± 2.0</td>
<td>12.0 ± 2.2*</td>
<td>30.9 ± 5.3</td>
<td>18.2 ± 3.7</td>
<td>14.1 ± 1.8*</td>
</tr>
<tr>
<td></td>
<td>PT/BW (%)</td>
<td>25.4 ± 1.4</td>
<td>18.6 ± 1.8</td>
<td>30.5 ± 9.0</td>
<td>24.0 ± 4.7</td>
<td>19.7 ± 2.7</td>
</tr>
<tr>
<td></td>
<td>AP (Watts)</td>
<td>40.2 ± 4.8</td>
<td>8.9 ± 3.6*</td>
<td>39.8 ± 8.4</td>
<td>19.0 ± 5.9</td>
<td>16.2 ± 3.3*</td>
</tr>
<tr>
<td><strong>Left Knee</strong></td>
<td>PT (FT-LBS)</td>
<td>27.3 ± 1.9</td>
<td>11.9 ± 2.2*</td>
<td>29.9 ± 5.4</td>
<td>15.0 ± 2.6*</td>
<td>17.0 ± 2.5</td>
</tr>
<tr>
<td></td>
<td>PT/BW (%)</td>
<td>25.6 ± 1.4</td>
<td>17.0 ± 1.7*</td>
<td>30.0 ± 9.6</td>
<td>19.6 ± 2.8</td>
<td>24.8 ± 6.1</td>
</tr>
<tr>
<td></td>
<td>AP (Watts)</td>
<td>39.8 ± 4.5</td>
<td>8.3 ± 3.1*</td>
<td>37.4 ± 8.1</td>
<td>18.7 ± 5.8</td>
<td>23.7 ± 5.0</td>
</tr>
</tbody>
</table>

* p<0.05 significantly different than controls; † p<0.05 significantly different than MPS-IH
MPS-IH, mucopolysaccharidosis I Hurler syndrome; MPS-IA, mucopolysaccharidosis I attenuated; MPS-II, mucopolysaccharidosis II; MPS-VI, mucopolysaccharidosis VI; PT, peak torque; PT/BW, peak torque per unit body weight; AP, average power
Figure Caption

Figure 1. Dominant leg extension average peak torque in study population at 90, 120, and 180 degrees per second for controls (n=42) (solid circle), mucopolysaccharidosis I Hurler syndrome (n=12) (solid square), mucopolysaccharidosis I attenuated (n=6) (solid triangle), mucopolysaccharidosis II (n=8) (open circle), and mucopolysaccharidosis VI (n=4) (open diamond).
*Significantly ($p<0.05$) different than controls. †Significantly ($p<0.05$) different than MPS-IA.
Figure 1.