Secondary Muscle Pathology and Metabolic Dysregulation in Adults with Cerebral Palsy

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Cerebral Palsy as a Model

- Most common childhood onset physical disability
  - About 3/1,000 births*
- Primary condition non-progressive
- Life span to adult years, normal in less affected (GMFCS I-III)

Function

- Functional status as child predicts adulthood
- Decline is frequently, but not always seen
- Decline may relate to secondary factors
Walk and stairs at 10 → 23% decline
• Some walking, no w/c → some decline, some improvement
• W/C use → generally declined
• After 25 years old, little improvement, some decline
• Age 60-75, significant decline in ambulation, less so in speech and self feed
Well described pattern

- Opheim, 2009, DMCN
  - 7 year f/u on 1999 study
  - Reports of decreased walking function increased
    - 39% to 52%
    - Includes 37% with hemiplegia
    - Age of change
      - 37 years old for bilateral
      - 52 for unilateral
    - Associated with reports of pain and fatigue
Contributing Factors

- Pain and Fatigue
- Musculoskeletal problems (contractures, dislocations)
- Inadequate attention to function (no therapies)
- Accessibility—Inadequate access to care
- Poor levels of fitness
Fitness in Children & Adults with CP

- Decreased aerobic capacity
- Decreased strength
- Decreased flexibility
- Decreased levels of Physical Activity
  - Especially health-related PA
- Cardiovascular disease significant cause of death
  - Strauss 1999
- Risk of overweight and obesity
Muscle volume in CP

Noble et al., *Brain Develop*, 2014, 36(4): 294–300
Not only about age.

Children with QCP have more IMAT than typically developing children, and was found to be related to their low level of physical activity. Johnson et al. *J Pediatr*. 2009 May;154(5):715-20.

Separation of AT from MRI of the midthigh of a prepubertal girl with QCP and D-F, a typically developing prepubertal girl. A and D contain subcutaneous, subfascial, and intermuscular AT; B and E contain only subfascial and intermuscular AT; and C and F contain only IMAT.
Inter- and Intramuscular Fat in CP

Figure 2 Percentage IntraMF and IMAT in the medial gastrocnemius (MG), lateral gastrocnemius (LG), soleus (SOL), tibialis anterior (TA), tibialis posterior (TP) and in the BSCP group (white) and TD group (grey). IMAT and IntraMF in all muscles were significantly different between groups (p < 0.05). Error bars represent the standard error of each group.

Figure 5 Percentage intramuscular fat in the medial gastrocnemius (MG), lateral gastrocnemius (LG) and soleus (SOL) for the TD group (grey), the no intervention BSCP subjects (white) and the gastrocnemius recession BSCP subjects (striped).

Noble et al., *BMC Musc Disor*, 2014, 15:236
Analytic Morphomics in CP

CT scans were processed and analyzed for visceral fascial determination, and to draw contours of psoas major muscles at the L4 level

(a) a 53 year old, typically-developed male (65 kg body mass), and (b) a 54 year old male with CP (66 kg body mass).
Results

After controlling for age, sex, and body mass, adults with CP had

- Lower cortical BMD ($\beta=-63.41$ HU, $p<0.001$)
- Lower trabecular BMD ($\beta=-42.24$ HU, $p<0.001$)
- Smaller psoas major areas ($\beta=-374.51$ mm$^2$, $p<0.001$)
- Lower attenuation ($\beta=-9.21$ HU, $p<0.001$)
- Greater VAT areas ($\beta=3914.81$ mm$^2$, $p<0.001$)
- Greater SAT areas ($\beta=4615.68$ mm$^2$, $p<0.001$)
Muscle attenuation was significantly correlated with trabecular (r=0.51, p=0.002) and cortical (r=0.46, p=0.006) BMD; whereas VAT was negatively associated with cortical BMD (β=-0.037 HU/cm²; r²=0.13; p=0.03).
Importantly, this is not specific to CP

- N=4200
- Densities of muscles and bones were robustly and inversely associated with visceral adiposity
- Somewhat contrary to the widely-held belief about BMD and obesity

Not so Novel a Concept, but…

Sedentary Behavior

High Fat Diet

Aging
- Diminished Aerobic Capacity
- Sarcopenia
- Weakness
- Functional Deficit
- Fatigability

Impaired Myogenesis
- Physical & Cognitive Frailty
- Decreased Mitochondrial Density
- Muscular Fibrosis

Oxidative Stress
- Incomplete beta-oxidation
- Dyslipidemia

Inflammation
- Hyperglycemia
- Metabolic Inflexibility
- Impaired Insulin Signaling
- Altered Nutrient Partitioning

Cerebral Palsy
- Chronic Neural Inflammation
- Exaggerated Sedentary Behavior
- Abnormal Musculoskeletal Development
- Muscle Spasticity

Insulin Resistance
- Hypertension
- Impaired Insulin Signaling

Obesity
- Cardiovascular disease and type 2 diabetes

Muscle Pathology and Accelerated Functional Decline

Central Adiposity as a Risk Factor in CP

ORIGINAL ARTICLE

Predictors of Cardiometabolic Risk Among Adults With Cerebral Palsy
Mark D. Peterson, PhD, Heidi J. Hearpda, MD, Edward A. Hurvitz, MD


Objective. To examine the independent association between various anthropometric indicators and standard clinical markers of cardiometabolic health risk among adults with cerebral palsy (CP).

Design. Cross-sectional study.

Setting. Clinical center for CP treatment and rehabilitation.

Participants. Adults with CP (N=65) with a mean ±SD of 37±13.5 years, and Gross Motor Function Classification System (GMFCS) levels of I-V.

Interventions. None applicable.

Main Outcome Measures. Adults with CP were assessed for body mass index (BMI), waist circumference (WC), hip circumference (HC), waist-to-hip ratio (WHR), waist-to-height ratio (WHHR), and serum lipid profiles. Data were analyzed with multiple regression analysis and general linear models, and are reported as means ±SD.

Results. Mean BMI was 29.1±7.3 kg/m². BMI was not associated with any measures of cardiometabolic risk. Using GMFCS categories (2 groups: GMFCS levels I-III and IV-V), BMI was significantly lower among GMFCS levels IV-V (24.2±3.8 kg/m²) versus GMFCS levels I-III (30.1±3.6 kg/m²). WC and WHR were not correlated with any cardiometabolic outcomes. Conversely, measures of WHR were independently associated with various indices of risk, including total cholesterol to high-density lipoprotein (HDL) cholesterol ratio (r=−0.5; P<0.05), HDL cholesterol (r=−0.5; P<0.01), and triglycerides (r=0.6; P<0.01), suggesting that greater WHR was indicative of elevated risk.

Conclusions. It is likely that WHR represents a stronger predictor of risk, because this measure was robustly and independently associated with 3 primary clinical markers of cardiometabolic health in adults with CP.

Keywords. Anthropometry; body mass index; Cerebral palsy; hyperlipidemia; obesity; rehabilitation. © 2012 by the American Congress of Rehabilitation Medicine

List of Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>BMI</td>
<td>body mass index</td>
</tr>
<tr>
<td>CP</td>
<td>cerebral palsy</td>
</tr>
<tr>
<td>GMFCS</td>
<td>Gross Motor Function Classification System</td>
</tr>
<tr>
<td>HC</td>
<td>hip circumference</td>
</tr>
<tr>
<td>HDL-C</td>
<td>high-density lipoprotein cholesterol</td>
</tr>
<tr>
<td>LDL-C</td>
<td>low-density lipoprotein cholesterol</td>
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<tr>
<td>TCHol</td>
<td>total cholesterol</td>
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<tr>
<td>TG</td>
<td>triglycerides</td>
</tr>
<tr>
<td>VAI</td>
<td>visceral adipose tissue</td>
</tr>
<tr>
<td>WC</td>
<td>waist circumference</td>
</tr>
<tr>
<td>WHR</td>
<td>waist-to-hip ratio</td>
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<tr>
<td>WHHR</td>
<td>waist-to-height ratio</td>
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Arch Phys Med Rehabil Vol 93, May 2012
Abdominal obesity is an independent predictor of serum 25-hydroxyvitamin D deficiency in adults with cerebral palsy

Mark D Peterson*, Heidi J Haapala, Ashish Chaddha and Edward A Hurvitz

Figure 2 Partial residual scatter plot for the variables waist circumference (WC) and 25-hydroxyvitamin D after controlling for the effect of variables age, sex, and GMFCS (with 70% and 80% prediction ellipses).
N=1,036 Adults with CP

Prevalence of Various Chronic Diseases in CP

<table>
<thead>
<tr>
<th>Condition</th>
<th>Typically Developed</th>
<th>Cerebral Palsy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 2 Diabetes</td>
<td>7.1</td>
<td>18.5</td>
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<tr>
<td>Asthma</td>
<td>9.5</td>
<td>22.7</td>
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<tr>
<td>Hypertension</td>
<td>27.9</td>
<td>55.2</td>
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<tr>
<td>Other Heart Problems</td>
<td>10.7</td>
<td>30.4</td>
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<tr>
<td>Stroke</td>
<td>3.0</td>
<td>11.3</td>
</tr>
<tr>
<td>Emphysema</td>
<td>1.7</td>
<td>8.8</td>
</tr>
<tr>
<td>Joint Pain</td>
<td>28.0</td>
<td>47.3</td>
</tr>
<tr>
<td>Arthritis</td>
<td>21.1</td>
<td>58.8</td>
</tr>
</tbody>
</table>

Peterson, M, Ryan, J., Hurvitz, E. and Mahmoudi *In Review.*
After adjustment for:
- Age
- Sex
- Household Income
- Education
- Race/Ethnicity
- Type of Insurance
- Geographic Region
- Survey Year
- Self Reported Physical and Mental Health

<table>
<thead>
<tr>
<th>Condition</th>
<th>Adjusted Odds Ratio</th>
</tr>
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<tbody>
<tr>
<td>Diabetes</td>
<td>1.43</td>
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<tr>
<td>Asthma</td>
<td>1.88</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.54</td>
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<tr>
<td>Other Heart Problems</td>
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<tr>
<td>Stroke</td>
<td>1.84</td>
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<tr>
<td>Emphysema</td>
<td>2.22</td>
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<tr>
<td>Joint Pain</td>
<td>1.66</td>
</tr>
<tr>
<td>Arthritis</td>
<td>2.07</td>
</tr>
</tbody>
</table>

Fully Adjusted Model
Conceptual Model of Mechanisms & Targets

Transition from Childhood to Adulthood: Diminished function, decreased activity, chronic spasticity, pain, fatigue, and weakness

Exaggerated Sedentary Behavior
Reduced Functional Reserve

Weakness
Sarcopenia
Mitochondrial Density
Myogenic Potential

Aging

Various Local and Systemic Effects of Muscle Pathology, Metabolic Dysregulation and Inflammation

Mitochondrial Stress
- ROS: $O_2^-$ → $H_2O_2$
- Lipotoxicity
  - IMCL accumulation
  - DAGs, TGs, Acyl-CoAs
- Macrophage Infiltration
  - M1 Polarization
- Increased ECM transcripts
- Muscle Fibrosis
- Skeletal Muscle IR

FFA

Overnutrition
Physical Activity

Obesity

Increased Food Intake
Excess Nutrient Storage

Satellite Cell Content
Activation of FAP cells

Incomplete beta-oxidation
FFA/Lipid Flux > Demand

Adipose tissue hypertrophy/hyperplasia
ATM infiltration

Common Metabolic Tissue Inflammatory Activation Pathways

Inflammatory Genes
Nucleus

Cytokines

SFA

LPS
SFA

TNF-α

TLR, NLR

TNFR

TAB1

TAK1

MKK4

JNK

NFkB

AP-1

Individuals with CP are predisposed to various secondary health complications that may be directly “caused” by modifiable lifestyle factors such as exaggerated sedentary lifestyles and insufficient physical activity

Publication trends for the topic of physical activity or exercise training in cerebral palsy: 1955-2014.

*As of June 2014, there were 39 publications meeting inclusion criteria. At approximately 6.5 publications per month, this is the highest rate per year (i.e., in 2013 there was an average of 5.4 per month).
• Fundamental movement skills are the primary predictor of activity participation among children with CP, with those who are more proficient tending to be more physically active

• Habitual physical activity is directly associated with motor functional capacity, i.e., higher HPA levels associated with greater motor capacity.
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