Chronic Disease Risk among Adults with CP: The Role of Premature Aging, Obesity, and Sedentary Behavior

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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
Related to Early Status (Day, 2004)

- 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

• Several other articles describe loss of ambulation
  – Ando, 2000, Clin Rehab
    • Surveyed adults in supported work environment
    • 35% reported deterioration of function
      – Includes 23% of “no device” (Presumably GMFCS I or II)
      – 43% of with device (GMFCS III)
    • High rates in third and fourth decade
    • Suggested a relationship to work environment
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
Well Describe Pattern

• Krakovsky 2007 Research in Developmental Disabilities
  – Small study, but looked at several factors associated with functional loss
  – Only age was significant—oldest patient 29

• Kembhavi DMCN 2011
  – Review paper
  – Identified 9 studies examining functional deterioration
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 Adults with CP

- Risk of overweight
  - Cardiac Risk?
- Decreased aerobic capacity
- Decreased strength
- Decreased flexibility
- Decreased levels of Physical Activity
  - Especially health-related PA
- Cardiovascular disease significant cause of death
  - Stauss 1999
Simulation Modeling for the Future

• Predictions for 2030 suggest that 50% of the population will be obese...

• Thus accruing an additional
  – 6–8.5 million cases of diabetes,
  – 5.7–7.3 million cases of heart disease and stroke
  – 492,000–669,000 additional cases of cancer*
  – 26–55 million quality-adjusted life years (QALY) forgone


*For every 5 kg/m² in BMI increases a man’s risk of oesophageal cancer by 52% and for colon cancer by 24%, and in women, endometrial cancer by 59%, gall bladder cancer by 59%, and postmenopausal breast cancer by 12%
Resulting in....

- Increased medical costs associated with treatment of these preventable diseases by $48-66 billion **PER YEAR** in the US by 2030.

Body Mass Index (BMI): A Good Proxy for Obesity

- Body Mass Index = wt/ ht²
- Utility of BMI is particularly relevant to Cross-sectional research
  - RISK of disease increases when BMI increases
- However...
A “sensitivity” issue...

• What we see on the surface or read from the scale is merely a glimpse of the truth

• BMI does not discriminate adipose tissue and muscle, and lacks sensitivity to identify non-obese individuals with excess body fat.

  – Okorodudu et al. *Int J Obes.* 2010
Obesity Misclassification

Body Mass Index (kg·m$^{-2}$)

Female
Male
Obesity misclassification in motor disabilities

![ROC Curves for Comparisons](a)  
**ROC Curve (Area)**
- bmi (0.9182)
- BMI=25 (0.8317)
- BMI=27 (0.8218)
- BMI=29 (0.7727)
- BMI=31 (0.7049)
- chance (0.5000)

![ROC Curves for Comparisons](b)  
**ROC Curve (Area)**
- bmi (0.9168)
- BMI=25 (0.8517)
- BMI=27 (0.7877)
- BMI=29 (0.7756)
- BMI=31 (0.7310)
- chance (0.5000)
BMI is not associated with dyslipidemia in CP

- Waist-to-hip ratio (WHR) was independently associated with various indices of cardiometabolic risk, including total cholesterol to HDL-cholesterol ratio, HDL-cholesterol, and triglycerides.

**Conclusions:** WHR represents a strong predictor of risk, as this measure was independently associated with 3 primary clinical markers of cardiometabolic health in adults with CP
- In contrast to BMI, WC, HC and WtHR, which were not associated with any markers of risk, and were influenced by GMFC

Current Focus: Predictors, Confluence and Consequences of Frailty and Obesity in Motor Disabilities

Healthy Patient

Average Patient

Cerebral Palsy

Peterson (PI): 1K01HD074706-01, R24 HD065702
When Muscle Turns to Fat...

25 Years Old

65 Years Old

Goodpaster et al, 2006
"Muscle Attenuation"

- An altered skeletal muscle composition in aging and obese individuals is manifest by a reduced attenuation coefficient on CT (HU)
- Associated with a reduced oxidative enzyme capacity, weakness, and IR in muscle.

Intermuscular adipose tissue (IMAT) and Intramyocellular Lipid (IMCL)

Also develop as a feature of:
• Disease processes (e.g. DMD, T2DM)
• Spinal cord injury
• Sarcopenia ("sarcopenic obesity")
• Obesity
• Prolonged sedentary behavior*

Muscle and Bone Quality in CP

Peterson, MD, et al. In Review.
## Preliminary Results

<table>
<thead>
<tr>
<th></th>
<th>Age</th>
<th>Psoas HU</th>
<th>Psoas Area</th>
<th>Lean Psoas</th>
<th>BMD</th>
<th>VAT</th>
<th>SAT</th>
<th>Total Body Area</th>
<th>Fascia Area</th>
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<tbody>
<tr>
<td>Age</td>
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<td>-0.217</td>
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<td>0.972*</td>
<td>0.094</td>
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<td>0.221</td>
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<tr>
<td>Total Body Area</td>
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<td>0.767*</td>
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<tr>
<td>Fascia Area</td>
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</table>

*significant at P<0.05.
Correlation between Psoas density and BMD at L4

\[ y = 1.7544x + 107.29 \]

\[ R^2 = 0.1479 \]
Remains Significant after controlling for the effect of age and gender
**Triple-Whammy Effect**

- Thus, in conjunction with increased skeletal stress and the handicap of moving dead weight adipose tissue, the negative impact of IMAT on MQ leads to gradual declines in functional status, reduced PA participation due to increased fatigue, and even *more* weight gain.

- Why?! What is the mechanism?
Morphologic and metabolic events of sedentary, obesity, and aging:
- Storage of “ectopic” adiposity (i.e. “steatosis”) in liver and muscle
- Decreased insulin sensitivity, and eventual IR & frank T2D
- Chronic and aberrant inflammation
- Decreased SM mitochondrial biogenesis and density
  - Decreased or incomplete beta-oxidation = lipotoxicity
- Increased mitochondrial “oxidative stress”
  - Increased formation of the free-radical superoxide (O$_2^-$), and subsequent H$_2$O$_2$ emission (i.e. ROS)
- And... Decreased Muscle Regenerative Capacity
  - Decreased Muscle Stem Cell density and myogenic lineage
  - And altered lineage to form fibrocyte/adipocytes
Not so novel concept, however to date...

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

Common Metabolic Tissue Inflammatory Activation Pathways

- LPS
- SFA
- TLR, NLR
- TNF-α
- TAB1
- TAK1
- MKK4
- IKKβ
- JNK
- NF-κB
- AP-1
- Inflammatory Genes
- Nucleus

Macrophage Infiltration
- M1 Polarization
- Increased ECM transcripts
- -Muscle Fibrosis
- Skeletal Muscle IR

NLRP3 Inflammasome
- IL-1β
- Phosphorylation of IRS1

Mitochondrial Stress
- ROS: O₂ → H₂O₂
- Lipotoxicity
  - IMCL accumulation
  - DAGs, TGs, Acyl-CoAs
- Macrophage Infiltration
  - M1 Polarization
- Increased ECM transcripts
- -Muscle Fibrosis
- Skeletal Muscle IR

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

- Mitochondrial Density
- Myogenic Potential
- Weakness
- Sarcopenia
- Satellite Cell Content
- Activation of FAP cells
- Incomplete beta-oxidation
- FFA/Lipid Flux > Demand
- Adipose tissue hypertrophy/hyperplasia
- ATM Infiltration

Overnutrition
- Physical Activity
- Obesity
- Increased Food Intake
- Excess Nutrient Storage

Exaggerated Sedentary Behavior
- Reduced Functional Reserve

Excessive Physical Activity

Hypothalamic Inflammation

Peterson, MD. AJP-Endo Metab. 2012 303(9):E1085-93.
BUT... Since *Sedentary Behavior* is associated with:

- Muscle weakness and atrophy, bone deterioration, diminished ROM, gross motor dysfunction, cardiometabolic decline, decreased QoL, depression, and early all-cause mortality (independent of body mass index)

- Most experts believe it simply boils-down reducing sedentary lifestyle
Sedentary behavior (SB)

• Indeed, time spent sitting correlates with an elevated risk of mortality for all causes and for cardiovascular disease
  • Dose-response relationship

• Sitting seems to have be associated with mortality independent of leisure time physical activity levels

• Thus, physical activity cannot compensate for high amounts of sitting

SB, MVPA and Metabolic Obesity: The General Population

Prevalence, %

<table>
<thead>
<tr>
<th>Low SB</th>
<th>Moderate SB</th>
<th>High SB</th>
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</thead>
<tbody>
<tr>
<td>High MVPA</td>
<td>9.6</td>
<td>6.6</td>
</tr>
<tr>
<td>Mod MVPA</td>
<td>16.1</td>
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<tr>
<td>Low MVPA</td>
<td>24.0</td>
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<tr>
<td>High MVPA</td>
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<td>15.1</td>
</tr>
<tr>
<td>Mod MVPA</td>
<td>15.1</td>
<td>21.0</td>
</tr>
</tbody>
</table>

Peterson, MD. et al. MSSE In Review
Moderate-to-vigorous activity time in adolescents with CP by GMFCS

What are the options?

• A simplistic preventive strategy is to encourage a lifestyle characterized by increasingly fragmented sedentary behavior.

• Thereafter reinforcing moderate and even vigorous PA is important to reduce the risk of metabolic obesity.
Thank you

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