The Progressive Development of Defining Pediatric Metabolic Syndrome

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HN&F 512
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Outline

- Background on Metabolic Syndrome (MetS)
- Adult MetS Definition(s)
- Challenges of Pediatric MetS
- Prevalence of Pediatric MetS
- Obesity
- Prevention/Treatment
- Future Research Aims
Background

- Introduced in 1988 by Reaven
- A combination of several metabolic risk-factors for cardiovascular disease in one individual, including:
  - Obesity
  - Insulin resistance
  - Glucose intolerance
  - Hypertension
  - Hyperlipidemia

<table>
<thead>
<tr>
<th></th>
<th>WHO</th>
<th>NCEP</th>
<th>IDF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definition</td>
<td>Diabetes, IFG, IGT or IR plus 2 or more of the following:</td>
<td>Exhibiting any 3 of the following:</td>
<td>Central obesity (WC) plus 2 or more of the following:</td>
</tr>
<tr>
<td>Glucose</td>
<td>≥ 110 mg/dL</td>
<td>≥ 100 mg/dL</td>
<td>≥ 100 mg/dL</td>
</tr>
<tr>
<td>Metabolism</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adiposity</td>
<td>WHR Males: &gt; 0.90 Females: &gt; 0.85 BMI ≥ 30</td>
<td>WC Males: &gt; 102 cm Females: &gt; 88 cm</td>
<td>WC Males: ≥ 102 cm Females ≥ 88 cm</td>
</tr>
</tbody>
</table>

**Main differences found in adiposity measure and glucose metabolism**
Challenges in Pediatrics

- Puberty and growth\textsuperscript{1,2,3}
  - Adipose tissue deposition, glucose and lipid metabolism
  - Insulin levels $\uparrow$ with onset of puberty
- Gender\textsuperscript{1}
- Ethnicity\textsuperscript{1,2,3}
- Body composition\textsuperscript{1}
- Environmental factors\textsuperscript{1}
  - Tobacco smoke exposure
- Lifestyle factors\textsuperscript{1}
  - Physical inactivity, alcohol consumption

Ethnicity

• Lipid values of African American children have different distributions in comparison to Caucasians

• Type II diabetes is more common in children and adolescents from ethnic minorities

• Individuals with comparable BMI of different ethnic backgrounds may have significantly different body compositions

# Modifications of Adult Definitions

Table 2: Major and minor concerns for the adoption of the adult metabolic syndrome definition in children and adolescents

<table>
<thead>
<tr>
<th>Major</th>
<th>Minor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not enough evidence from longitudinal studies on the additional health risk of MS to obesity</td>
<td>Not enough information on tracking and long-term risk from childhood into adulthood</td>
</tr>
<tr>
<td>No information on family and individual history</td>
<td>No inclusion of ‘low-grade inflammation’ markers</td>
</tr>
<tr>
<td>No inclusion of fasting insulin level as an early marker of glucose homeostasis / metabolism disturbances</td>
<td>No information on non-alcoholic fatty liver disease</td>
</tr>
<tr>
<td>No estimation of adipose tissue related hormones/biomarkers</td>
<td>No information on environmental risk factors</td>
</tr>
<tr>
<td>No estimation of pubertal status</td>
<td></td>
</tr>
<tr>
<td>No available age-, gender- or race-specific reference values for all characteristics</td>
<td></td>
</tr>
<tr>
<td>Low sensitivity and specificity of obesity criteria (BMI and/or WC) in obese subjects</td>
<td></td>
</tr>
<tr>
<td>Equivalent value given to different items</td>
<td></td>
</tr>
<tr>
<td>No evidence on the cumulative health-related risk associated with the number of criteria</td>
<td></td>
</tr>
<tr>
<td>No specific treatment for the MS</td>
<td></td>
</tr>
<tr>
<td>DM2 considered a risk-factor instead of an established disease</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: BMI, body mass index; DM2, diabetes mellitus type 2; MS, metabolic syndrome; WC, waist circumference.
Are prevalence reports of pediatric MetS inconsistent?
Comparing Four Different Definitions of MetS

- N = 251 (age not provided)
  - 122 African Americans
  - 129 Caucasians

- In 2008, Lee et al. compared MetS definitions used in previous studies by:
  - Weiss et al
  - Cook et al
  - Ford et al
  - Cruz et al

<table>
<thead>
<tr>
<th></th>
<th>Obesity</th>
<th>BP</th>
<th>TGs</th>
<th>HDL-C</th>
<th>Glucose intolerance*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Weiss et al</strong></td>
<td>BMI z score ≥ 2 for age and sex</td>
<td>&gt; 95th p for age, sex and height</td>
<td>&gt; 95th p for age, sex and race</td>
<td>&lt; 5th p for age, sex and race</td>
<td>IGT</td>
</tr>
<tr>
<td><strong>Cook et al</strong></td>
<td>WC ≥ 90th p for age and sex</td>
<td>≥ 90th p for age, sex and height</td>
<td>≥ 100 mg/dL</td>
<td>≤ 40 mg/dL</td>
<td><strong>FPG ≥ 110</strong> mg/dL or IGT</td>
</tr>
<tr>
<td><strong>Ford et al</strong></td>
<td>WC ≥ 90th p for age and sex</td>
<td>≥ 90th p for age, sex and height</td>
<td>≥ 100 mg/dL</td>
<td>≤ 40 mg/dL</td>
<td><strong>FPG ≥ 100</strong> mg/dL or IGT</td>
</tr>
<tr>
<td><strong>Cruz et al</strong></td>
<td>WC ≥ 90th p for age, sex and race</td>
<td>&gt; 90th p for age, sex and height</td>
<td>≥ 90th p for age and sex</td>
<td>≤ 10th p for age and sex</td>
<td>IGT</td>
</tr>
</tbody>
</table>

IGT = impaired glucose tolerance  
FPG = fasting plasma glucose  
*p = percentile
### Results

<table>
<thead>
<tr>
<th>Definition</th>
<th>Prevalence of MetS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weiss et al.</td>
<td>18.7%</td>
</tr>
<tr>
<td>Cook et al.</td>
<td>21%</td>
</tr>
<tr>
<td>Cruz et al.</td>
<td>13.4%</td>
</tr>
<tr>
<td>Ford et al. *</td>
<td>25.1%</td>
</tr>
</tbody>
</table>

*N = 186*

* A lower threshold of fasting glucose (≥ 100 mg/dL) was proposed by Ford et al.

IDF definition versus Weiss et al

- **N = 528 overweight/obese children (3-16 years)**

<table>
<thead>
<tr>
<th></th>
<th>MetS-Child (Weiss et al)</th>
<th>MetS-Adolescent (IDF)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>All age groups</td>
<td>&gt; 10 years (10-16)</td>
</tr>
<tr>
<td><strong>Obesity</strong></td>
<td>BMI ≥ 97&lt;sup&gt;th&lt;/sup&gt; p</td>
<td>90&lt;sup&gt;th&lt;/sup&gt; p for WC</td>
</tr>
<tr>
<td><strong>Glucometabolic disorder</strong></td>
<td>Impaired glucose tolerance: 2 hr glucose ≥ 7.8 and &lt; 11.0 mmol/L</td>
<td>Impaired Fasting Glucose: FG ≥ 5.6 mmol/L or Diabetes (2h-plasma glucose ≥ 11.0 mmol/L)</td>
</tr>
<tr>
<td><strong>HDL-cholesterol</strong></td>
<td>&lt; 5&lt;sup&gt;th&lt;/sup&gt; p for age and sex</td>
<td>&lt; 1.03 mmol/L</td>
</tr>
<tr>
<td><strong>Triglycerides</strong></td>
<td>&gt; 95&lt;sup&gt;th&lt;/sup&gt; p for age and sex</td>
<td>≥ 1.7 mmol/L</td>
</tr>
<tr>
<td><strong>Blood pressure</strong></td>
<td>Systolic and diastolic &gt; 95&lt;sup&gt;th&lt;/sup&gt; p for height and sex</td>
<td>Systolic ≥ 130 mmHg and/or diastolic ≥ 85 mmHg</td>
</tr>
</tbody>
</table>

p = percentile

Results

- Prevalence of MetS-child within the sample was 18.6%.

<table>
<thead>
<tr>
<th>Children &lt; 10 years</th>
<th>Children 10-16</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>14.1%</td>
<td>20.7%</td>
<td>0.073</td>
</tr>
</tbody>
</table>

- In children > 10 years, prevalence of MetS-adolescent was higher than MetS-child.

<table>
<thead>
<tr>
<th>MetS-adolescent</th>
<th>MetS-child</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>33.2%</td>
<td>20.7%</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>
Overall, MetS-adolescent (proposed by the IDF) found the greatest prevalence of MetS

MetS-child was highly prevalent in overweight/obese children and adolescents

A higher prevalence existed with MetS-adolescent criteria
  - WC may serve as a better predictor of MetS
NCEP ATP III versus Weiss et al

- **N = 100, ages 6 to 16 years**
  - **BMI > 85\(^{th}\) percentile for age and sex**

<table>
<thead>
<tr>
<th></th>
<th>Weiss et al</th>
<th>NCEP ATP III</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Glucose</strong></td>
<td>FPG ≥ 100 mg/dL</td>
<td>FPG ≥ 100 mg/dL</td>
</tr>
<tr>
<td><strong>WC</strong></td>
<td>WC ≥ 75(^{th}) p for age and sex</td>
<td>WC ≥ 75(^{th}) p for age and sex</td>
</tr>
<tr>
<td><strong>TGs</strong></td>
<td>TGs ≥ 95(^{th}) p for age and sex</td>
<td>Fasting TGs ≥ 100 mg/dL</td>
</tr>
<tr>
<td><strong>HDL-C</strong></td>
<td>HDL &lt; 5(^{th}) p for age and sex</td>
<td>HDL &lt; 50 mg/dL &lt; 45 mg/dL in males &gt; 15y</td>
</tr>
<tr>
<td><strong>BP</strong></td>
<td>SBP/DBP &gt; 95(^{th}) p for age and sex</td>
<td>SBP/DBP &gt; 90(^{th}) p for age and sex</td>
</tr>
</tbody>
</table>

\( p = \text{percentile} \)

### Results

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<thead>
<tr>
<th></th>
<th>NCEP ATP III</th>
<th>Weiss et al</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total (n)</td>
<td>Overweight</td>
</tr>
<tr>
<td>High TGs</td>
<td>74</td>
<td>16/20</td>
</tr>
<tr>
<td>Low HDL-C</td>
<td>70</td>
<td>15/20</td>
</tr>
<tr>
<td>High WC</td>
<td>81</td>
<td>11/20</td>
</tr>
<tr>
<td>High SBP/DBP</td>
<td>36</td>
<td>8/20</td>
</tr>
<tr>
<td>High FBS</td>
<td>12</td>
<td>1/20</td>
</tr>
</tbody>
</table>

FBS = fasting blood sugar

63 met criteria for MetS defined by NCEP ATP III
39 met criteria for MetS defined by Weiss et al
Summary

- Prevalence of MetS in children and adolescents depends on:
  - Criteria used
  - Specific cut-points

- ↑ risk of MetS in overweight/obese children and adolescents, regardless of criteria
How do we measure overweight/obesity for children and adolescents?
Body Mass Index (BMI)

BMI (percentile) | Classification
---|---
≥ 85\textsuperscript{th} | Overweight
≥ 95\textsuperscript{th} | Obese

Example:
- 10 year old male
- Wt = 140 lbs  Ht = 64 in (5 ft 4 in)
- BMI = 24 kg/m\textsuperscript{2}

## Waist Circumference (WC)

### Example:
- 10 year old male
- WC = 72.0 cm
- WC > 75th percentile

Some researchers believe WC is less reliable in children and adolescents due to puberty and racial or ethnic differences.

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Body Fat Distribution

- Body fat in the intra-abdominal (visceral) region of children and adolescents is an important determinant of MetS risk in adulthood\(^1,2\)

16.9% of children aged 2 through 19 years were obese in 2009-2010

31.8% were either overweight or obese

12.3% were ≥ the 97th percentile of BMI for age
  - Classified as severely obese

Obesity was significantly higher among males
  - 18.6% vs. 15.0%, p = 0.01

21.2% of non-Hispanics and 14.0% non-Hispanic whites were obese

Obesity Health Concerns

- Increased blood pressure
- Increased triglycerides
- Decreased HDL cholesterol
- Abnormal glucose metabolism
- Insulin resistance
- Inflammation
- Compromised vascular function

T2DM → T2DM → ↑ BP → ↑ TGs → ↑ IR → ↑ BG → Inflammation → ↑ LDL-C → ↓ HDL-C → CVD
Prevention & Treatment

- Decrease weight if overweight or obese\(^2\)

- NOTE: MetS risk criteria has been observed in children of normal weight\(^1\)

- Careful evaluation and follow-up is needed when any risk criteria is present in this age group\(^2\)

- Lifestyle modifications\(^2\)
  - Diet
  - Physical activity

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Conclusion

• Prediction of adult disease limited
  ◦ Lack of longitudinal data

• Inconsistency in prevalence
  ◦ Multiple definitions used in same group of children

• Pediatricians should assess the following parameters from the age of 3 years:
  ◦ Height
  ◦ Weight
  ◦ Blood pressure

• If overweight or obese, a closer evaluation should take place
  ◦ Protocols yet to be established
  ◦ Blood work?

Future Research Aims

- Large, diverse samples
- Longitudinal design
- Identify most effective adiposity measure
- Uniform definition of MetS
- Protocols needed for:
  - Prevention
  - Early recognition
  - Effective treatment
Questions?