Management of Adolescent Metabolic Syndrome

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Objective:

• Describe the diagnosis and management of metabolic syndrome (MetS) in youth.
  – Diagnostic challenges
  – Prevalence estimates
  – NHLBI 2011 Guidelines for management
  – Economic aspects
A Global Definition of MetS:

“In adults] The metabolic syndrome is a constellation of interrelated risk factors of metabolic origin—metabolic risk factors—that appear to directly promote the development of atherosclerotic cardiovascular disease. Individuals with the metabolic syndrome also are at increased risk for developing type 2 diabetes mellitus.”

Youth vs. Adult

• The focus in youth is **primordial and primary prevention of atherosclerosis**, while prevention of progression of atherosclerosis and/or acute cardiovascular events is the focus in adults.
What is the utility of diagnosing MetS in youth?

- It may aid in the identification of high-risk youth with subclinical vascular damage.
- Compared to youth/adults without MetS at either age range, youth/adults with MetS had
  - 3.4 times the risk of high cIMT
  - 12.2 times the risk of T2DM in adulthood
- Resolution of MetS by adulthood showed similar risk to youth who never had MetS

C Magnussen et al JACC 2012;60:1631-1639.
What is the utility of diagnosing MetS in youth?

“...youth with multiple borderline risk factors might, in fact, have risk equivalent to a person with extreme abnormality of a single major risk factor.”

Longitudinal Impact of Risk Factors in Youth - Key Studies

- Bogalusa Heart Study\(^1\)
- Muscatine Study\(^2\)
- Childhood Determinants of Adult Health (CDAH)\(^3\)
- Cardiovascular Risk in Young Finns Study\(^4\)
- Pathological Determinants of Atherosclerosis in Youth (PDAY)\(^5\)
- International Childhood Cardiovascular Cohort Consortium\(^6\)
  - 6328 subjects 11.4±4.0 yrs. At baseline
  - Mean length of follow-up was 23.1±3.3 yrs.

\(^2\) Davis PH et al Circulation 2001;104:2815-9
\(^3\) Magnussen CG Circulation 2008;117:32-42
\(^4\) Raitakari OT JAMA 2003;290:2277-83
\(^5\) JAMA 1999;281:727-735
Bogalusa Heart Study: Impact of Multiple Risk Factors (smoking, ≥75%tile for TC/HDL-C, WC, SBP, insulin) on IMT
Right Coronary Artery Raised Lesions by Age and Number of Risk Factors, Men
PDAY Study

No. Risk Factors

Surface Area Involved (%)

Age (y)

15-19 20-24 25-29 30-34

0 2 4 6 8 10

0 1 2 3 4+

Courtesy of S. Gidding
NHLBI 2011 Guidelines
Metabolic Syndrome

• “Because of the paucity of evidence, recommendations are a consensus of the Expert Panel.” (*Grade D)
• The Expert Panel concluded that MetS should NOT be considered as a separate risk factor.
• MetS is NOT included as a high risk condition in contrast to the adult NCEP guidelines.

*Grade D: Expert opinion, case reports, or reasoning from first principles (bench research or nonhuman animal studies)
Developing A Working Definition:

• Many different definitions in youth have been used to diagnose metabolic syndrome (MetS).
  – Obesity vs insulin resistance as a prerequisite
  – Fasting glucose vs. insulin resistance
  – Different cutoffs for defining abnormal values

• The absence of a uniform definition is a roadblock to identifying the appropriate screening test(s), measuring prevalence, and establishing treatments.

Friend A et al, Metabolic Syndrome and Related Disorders, 2012 Dec 18
Component Definition is Closely Linked to Pediatric Pathophysiology

**Diagram:**
- Type 2 diabetes mellitus
- Dyslipidemia
- Hypertension
- Acanthosis nigricans
- PCOS NAFLD
- Pcos
- NAFLD
- NAFLD

**KEY:**
- SGA: Children born small for gestational age
- LGA: Children born large for gestational age
- GDM: Children born to mothers with gestational diabetes
- IGT: Impaired glucose tolerance
- IFG: Impaired fasting glucose
- PCOS: Polycystic ovarian syndrome
- NAFLD: Nonacoholic fatty liver disease
A diagnostic challenge unique to the pediatric population are the dynamic and multi-faceted metabolic and lifestyle factors that occur with growth and maturation.

- These age-related changes hinder the use of singular cut points to define MetS.
- Independent of the definition used, there is a flux in the diagnosis over time.
Changes in Body Composition

BMI=body mass index; LBM=lean body mass
Changes in Lipid Levels and Blood Pressure

Proportions of participants with persistent (aged 24-41 years), baseline only (aged 9-18 years) and incident MetS according to different definitions of MetS. Data from the Bogalusa Heart Study and Young Finns Study.
# NHLBI 2011 Diagnostic Criteria for MetS in Youth

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Cut Points</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Obesity</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td>≥85th to &lt;95th %tile</td>
<td><a href="http://www.cdc.gov/growthcharts/">www.cdc.gov/growthcharts/</a></td>
</tr>
<tr>
<td><strong>Blood Pressure</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>≥90th to &lt;95th %tile</td>
<td>Pediatrics 2004; 114(2 Suppl 4th Report):555-76</td>
</tr>
<tr>
<td><strong>Dyslipidemia</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HDL-C</td>
<td>≥40 to ≤45 mg/dL</td>
<td>NHLBI 2011 Guidelines for Lipids and Lipoproteins Pediatrics 2011;128:S1-S44</td>
</tr>
<tr>
<td>TG Age 0-9 yrs</td>
<td>≥75 to ≤100 mg/dL</td>
<td></td>
</tr>
<tr>
<td>TG Age ≥10 yrs</td>
<td>≥90 to ≤130 mg/dL</td>
<td></td>
</tr>
<tr>
<td>Non-HDL-C</td>
<td>≥120 to ≤140 mg/dL</td>
<td></td>
</tr>
<tr>
<td><strong>Glycemia</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fasting glucose</td>
<td>≥100 to &lt;126 mg/dL</td>
<td>ADA Screening Guidelines</td>
</tr>
<tr>
<td>Fasting Insulin</td>
<td>Elevated levels above normal for gender,race, pubertal status</td>
<td></td>
</tr>
</tbody>
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Can Non-HDL-C Levels Alone Be Used to Diagnose MetS?
ROC Curve Analysis of Non-HDL-C for Mets Among US Youth aged 12-19 years, NHANES 1999-2004

<table>
<thead>
<tr>
<th></th>
<th>AUC</th>
<th>95% CI</th>
<th>Optimal Non-HDL-C cutoff point, mg/dL</th>
<th>Sensitivity %</th>
<th>Specificity %</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCEP/ATP III-peds</td>
<td>0.77*</td>
<td>0.73-0.81</td>
<td>120</td>
<td>75</td>
<td>69</td>
</tr>
<tr>
<td>NCEP/ATP III-adult</td>
<td>0.81</td>
<td>0.76-0.86</td>
<td>120</td>
<td>73</td>
<td>75</td>
</tr>
<tr>
<td>IDF-peds</td>
<td>0.79</td>
<td>0.74-0.84</td>
<td>120</td>
<td>68</td>
<td>75</td>
</tr>
<tr>
<td>IDF-adult</td>
<td>0.78*</td>
<td>0.73-0.83</td>
<td>125</td>
<td>67</td>
<td>75</td>
</tr>
</tbody>
</table>

* P ≤ 0.05

Chaoyang Li, Earl S. Ford, Patrick E. McBride, Peter O. Kwiterovich, Brian W. McCrindle, Samuel S. Gidding
2011 NHLBI Recommendations

• Screen obese youth for standard CV risk factors in obese youth as well as evaluation of:
  – Liver function (NAFLD)
  – Sleep apnea
  – Left ventricular hypertrophy

• In the presence of any additional risk factor, treatment is aimed at therapeutic lifestyle changes.
  – Intensive weight reduction
  – CHILD 2-TG diet
  – Pharmacologic treatment of any additional risk factor according to guidelines
Prevalence of MetS

- Underuse of ICD-9 coding for obesity in children (or adults) makes it challenging to estimate obesity-associated conditions and economic consequences.
  - In 2005 only 1.7% of hospitalizations of 2 – 19 year olds had a diagnosis of obesity compared to prevalence of 18.1% from NHANES 2007-2008.
- The low rate of ICD-9 documentation suggests that the burden of childhood obesity is vastly underestimated.

## Prevalence Estimates

### Median and Range

<table>
<thead>
<tr>
<th></th>
<th>ATP</th>
<th>WHO</th>
<th>IDF</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All</strong></td>
<td>4.2% (1 – 19.2%)</td>
<td>6% and 18%</td>
<td>3.1% (1 – 14%)</td>
</tr>
<tr>
<td><strong>Overweight</strong></td>
<td>10.7% (2.8 – 37%)</td>
<td>x</td>
<td>6.7%</td>
</tr>
<tr>
<td><strong>Obese</strong></td>
<td>30.2% (2.1 – 50%)</td>
<td>26.1% (23.3 – 42.3%)</td>
<td>23.2% (16.4 – 44.2%)</td>
</tr>
</tbody>
</table>

Friend A et al in Metabolic Syndrome and Related Disorders Dec 2012
Recovery
The Importance of Interventions in Youth

• Overweight or obese children who were obese as adults had increased risks of T2DM, HTN, dyslipidemia, and carotid-artery atherosclerosis (i.e., increased cIMT).

• The risks of these outcomes among overweight or obese children who became nonobese by adulthood were similar to those among persons who were never obese.

M Juonala et al NEJM 2011;365:1876-85
Treatment Approaches

**Population Oriented**
- Focus on prevention through environmental & policy change (upstream approach)
- Broadest reach, critical for reaching most vulnerable population
- Best outcome if implemented in infancy

**Individual Oriented**
- Focus on treatment (downstream approach)
- Most familiar to health professionals
- Healthcare system is not well-suited to meet the long-term needs of obese children

NHLBI Diet for High TG or Non-HDL-C
CHILD-2-TG Diet

• 25–30% of calories from fat, <7% from saturated fat, ~10% from monounsaturated fat; <200 mg/d of cholesterol; avoid trans fats as much as possible. (Grade B)

• Decrease sugar intake (Grade A):
  – Replace simple with complex carbohydrates
  – No sugar sweetened beverages

• Increase dietary fish to increase omega-3 fatty acids (Grade D)

• If child is obese, nutrition therapy should include calorie restriction, and increased activity (beyond that recommended for all children) should be prescribed.

Summary Report: Pediatrics 2011;128:S1-S44
Pharmacotherapy

If exercise could be packaged in a pill it would be the most widely prescribed and beneficial medicine in this nation.

R. Butler
Economic Burden

• In a 2005 cost estimate of MetS in adults, Williams noted the cost was equal to or greater than that of T2DM resulting in **20-41% of US healthcare budget devoted to adults with MetS**.

• Ma and Frick* estimated lifetime medical cost related to obesity in youth using a simulation model to estimate the break-even point for interventions between ages 0 - 6 years, ages 7 - 12 years, and 13 - 18 years.

• They concluded that “...preventions targeting high-risk children, such as children with obese parents or from disadvantaged backgrounds, could achieve better results than those offering service to the whole population of children.”

• “Targeted interventions could yield higher cost savings than population-based interventions for young children (aged 0-6 years), whereas a population-based approach could yield greater economic net benefits for adolescents (aged 13-18 years).”

Conclusions

• Prevention of the metabolic syndrome is likely the best therapeutic approach
  – Infants and children who are crossing weight percentiles are at the highest risk.

• Treat children and adolescents with the metabolic syndrome aggressively with early nutritional changes and exercise.

• Use pharmaceutical therapy for CVD risk factors according to 2011 NHLBI guidelines if lifestyle changes are not effective in order to delay or prevent the cardiovascular sequelae.