Metabolic Syndrome and Polycystic Ovarian Syndrome in Adolescents

Adrienne M. Platt, MSN, CPNP
The Children’s Mercy Hospitals and Clinics
Section of Endocrinology
No Disclosures
Childhood Obesity

- Obesity in youth is epidemic in the United States (US) with 16.9% of 2-19 year olds meeting criteria [body mass index (BMI) ≥ the 95th % when plotted on the 2000 CDC growth charts] (Ogden, Carroll, Kit, & Flegal, 2012).

- Subsequent increase in insulin resistance, metabolic syndrome, and type-2 diabetes.


- Co-morbid alterations in health: insulin resistance, acanthosis nigricans, sleep apnea, Blount’s disease, hyperandrogenism, polycystic ovarian syndrome (PCOS), asthma, depression, low self-esteem, gallbladder disease, some cancers (Neef et al., 2013).
Health Impact of Obesity

According to the CDC in 2011:

• 26 million Americans have diabetes, with nearly a third undiagnosed

• Another 79 million have pre-diabetes (impaired fasting glucose or impaired glucose tolerance) and are likely to develop Type-2 diabetes if they do not alter their lifestyle habits

• The CDC projects that as many as 1 in 3 U.S. adults could have diabetes by 2050 if current trends continue.

• If obesity rates decreased by 1% from the predicted current trend, over the next two decades obesity related medical expenditures would decrease by 84.9 billion.

• If obesity prevalence had remained at the 2010 levels, the savings from obesity-related medical expenditures would have been $549.5 billion.
Identify Children at High Risk

- Excess weight for height. (50/50 child).
- Rapid weight gain.
- Family history of weight problems, type 2 diabetes, heart disease, HTN, abnormal lipids.
- Compare BMI to previous visit and plot the percentile on the 2000 CDC growth chart (Available via www.CDC.gov).
Causes of Insulin Resistance in Youth

- Major causes of peripheral insulin resistance:
  - Obesity
  - Genetics
  - Little physical activity
  - Diet
  - Ethnicity

(Santoro & Weiss, 2012).
Insulin Resistance

• Normal Response:
  • high glucose levels stimulate β cells to secrete insulin
  • decrease glucagon production leads to suppression of hepatic glucose production
  • increased glucose uptake in muscle, liver, and adipose tissue (Gallagher, Leroith, & Karnieli, 2011).

• Insulin Resistance:
  • β cell dysfunction occurs which causes a lack of a first phase insulin response to a glucose load.
  • The lack of insulin response results in a postprandial hyperglycemia
  • Causes an exaggerated 2nd phase insulin response.
  • Chronic hyperinsulinemia down-regulates insulin receptors which impairs insulin sensitivity (Gallagher, Leroith, & Karnieli, 2011).
Complications of Insulin Resistance

Excess Weight
Excessive Carbohydrate Intake
Sedentary Lifestyle
Genetics

Sleep Apnea
Polycystic Ovarian Disease
Increased blood clots risk.
Cardiomyopathy

Neurological Changes:
Urinary Frequency,
Lightheadedness,
Bloating, Heartburn,
Constipation and ED

Increase of Intra-Abdominal Fat
Elevated Blood Sugar
Hypertension (High Blood Pressure)

Atherosclerosis:
Contributes to Heart Attacks, Strokes and Peripheral Vascular Disease

Inflammation of the liver and cirrhosis.

Elevated Triglycerides
Low HDL - “Good Cholesterol”

www.google.com
Clinical Signs of Insulin Resistance

- Acanthosis nigricans and skin tags (joints, neck, axilla, skin folds)
- “hungry all the time” or “never full”
- Rapid weight gain (40 lbs in 4 months)
Adipose Tissue is an Organ

• Stores and releases energy in the form of triglycerides (excess food consumption or starvation)

• Endocrine organ, produces cytokines responsible for inflammation (IL-6, TNF-alpha, & adiponectin).

• In obese patients: increase IL-6, CRP, TNF-alpha, and a decrease in adiponectin and IL-10 induce a pro-inflammatory state resulting in insulin resistance.
Insulin Resistance to Metabolic Syndrome

• Bad genetics (get that family history!).
• Free Fatty Acids inhibit glucose uptake and metabolism which causes insulin resistance.
• Hepatic insulin resistance leads to up-regulated triglycerides.
• Visceral adiposity is associated with low HDLc levels.
• Obesity contributes to Metabolic Syndrome by increasing Free Fatty Acids and production of the inflammatory cytokines that lead to insulin resistance.
Metabolic Syndrome (MS)

- There has not been total agreement on the definition in children.
- Cook and colleagues (2003) adapted a definition from adult criteria (National Cholesterol Education Program (NCEP); Adult Treatment Panel III (ATP III). (Youth meeting 3 out of the 5 criteria= MS).

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Adults</th>
<th>Adolescents</th>
</tr>
</thead>
<tbody>
<tr>
<td>High Triglyceride Level mg/dl</td>
<td>≥ 150</td>
<td>≥ 110</td>
</tr>
<tr>
<td>Low HDL-C Level mg/dl</td>
<td>M: &lt; 40</td>
<td>M: ≤ 40</td>
</tr>
<tr>
<td></td>
<td>F: &lt; 50</td>
<td>F: ≤ 40</td>
</tr>
<tr>
<td>Abdominal Obesity cm</td>
<td>M: &gt; 102</td>
<td>≥ 90&lt;sup&gt;th&lt;/sup&gt; percentile for both</td>
</tr>
<tr>
<td></td>
<td>F: &gt; 88</td>
<td></td>
</tr>
<tr>
<td>High fasting glucose mg/dl</td>
<td>≥ 110</td>
<td>≥ 110</td>
</tr>
<tr>
<td>High blood pressure mm Hg</td>
<td>≥ 130/85</td>
<td>≥ 90&lt;sup&gt;th&lt;/sup&gt; percentile</td>
</tr>
</tbody>
</table>
Improvement in Risk Factors for Metabolic Syndrome and Insulin Resistance in Overweight Youth who are Treated with Lifestyle Intervention (2006)

- 49.5% of youth presented with multiple risk factors associated with metabolic syndrome at baseline (N = 109).

- 10% had impaired fasting glucose.

- Insulin resistance variables correlated significantly with factors associated with metabolic syndrome.

Monzavi et al., 2006
Metabolic Syndrome Criteria

• Waist Circumference (It is not as easy as it seems).

“measured using a steel measuring tape to the nearest 0.1 cm at the high point of the iliac crest at minimal respiration when the participant was in a standing position. The examiner stood behind the participant, palpated the hip area for the right iliac crest, marked a horizontal line at the high point of the iliac crest, and crossed the line to indicate the midaxillary line of the body (Fig 1). The examiner then stood on the participant’s right side and placed the measuring tape around the trunk in a horizontal flat surface at the level marked on the right side of the trunk. The recorder observed the participant to ensure that the tape was parallel to the floor and that the tape was snug but did not compress the skin”

Li, Ford, Mokdad, & Cook (2006), p. 1391
Waist Circumference in Children/Adolescents

<table>
<thead>
<tr>
<th>Age (y)</th>
<th>10th</th>
<th>25th</th>
<th>50th</th>
<th>75th</th>
<th>90th</th>
<th>10th</th>
<th>25th</th>
<th>50th</th>
<th>75th</th>
<th>90th</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>43.2</td>
<td>45.0</td>
<td>47.1</td>
<td>48.8</td>
<td>50.9</td>
<td>43.9</td>
<td>45.0</td>
<td>47.1</td>
<td>49.5</td>
<td>52.2</td>
</tr>
<tr>
<td>3</td>
<td>44.9</td>
<td>46.9</td>
<td>49.1</td>
<td>51.3</td>
<td>54.2</td>
<td>45.4</td>
<td>46.7</td>
<td>49.1</td>
<td>51.9</td>
<td>55.3</td>
</tr>
<tr>
<td>4</td>
<td>46.6</td>
<td>48.7</td>
<td>51.1</td>
<td>53.9</td>
<td>57.6</td>
<td>46.9</td>
<td>48.4</td>
<td>51.1</td>
<td>54.3</td>
<td>58.3</td>
</tr>
<tr>
<td>5</td>
<td>48.4</td>
<td>50.6</td>
<td>53.2</td>
<td>56.4</td>
<td>61.0</td>
<td>48.5</td>
<td>50.1</td>
<td>53.0</td>
<td>56.7</td>
<td>61.4</td>
</tr>
<tr>
<td>6</td>
<td>50.1</td>
<td>52.4</td>
<td>55.2</td>
<td>59.0</td>
<td>64.4</td>
<td>50.1</td>
<td>51.8</td>
<td>55.0</td>
<td>59.1</td>
<td>64.4</td>
</tr>
<tr>
<td>7</td>
<td>51.8</td>
<td>54.3</td>
<td>57.2</td>
<td>61.0</td>
<td>67.0</td>
<td>51.6</td>
<td>53.5</td>
<td>56.9</td>
<td>61.5</td>
<td>67.5</td>
</tr>
<tr>
<td>8</td>
<td>53.5</td>
<td>56.1</td>
<td>59.3</td>
<td>64.1</td>
<td>71.2</td>
<td>53.2</td>
<td>55.2</td>
<td>58.9</td>
<td>63.9</td>
<td>70.5</td>
</tr>
<tr>
<td>9</td>
<td>55.3</td>
<td>58.0</td>
<td>61.3</td>
<td>66.6</td>
<td>74.6</td>
<td>54.0</td>
<td>56.9</td>
<td>60.0</td>
<td>66.3</td>
<td>73.6</td>
</tr>
<tr>
<td>10</td>
<td>57.0</td>
<td>59.9</td>
<td>63.4</td>
<td>69.2</td>
<td>75.5</td>
<td>56.3</td>
<td>58.8</td>
<td>62.8</td>
<td>68.7</td>
<td>76.7</td>
</tr>
<tr>
<td>11</td>
<td>58.7</td>
<td>61.7</td>
<td>65.4</td>
<td>71.7</td>
<td>78.4</td>
<td>57.9</td>
<td>60.3</td>
<td>64.8</td>
<td>71.1</td>
<td>79.7</td>
</tr>
<tr>
<td>12</td>
<td>60.5</td>
<td>63.5</td>
<td>67.4</td>
<td>74.3</td>
<td>82.8</td>
<td>59.5</td>
<td>62.0</td>
<td>66.7</td>
<td>73.5</td>
<td>82.7</td>
</tr>
<tr>
<td>13</td>
<td>62.2</td>
<td>65.4</td>
<td>69.5</td>
<td>76.8</td>
<td>84.2</td>
<td>61.0</td>
<td>63.7</td>
<td>68.7</td>
<td>75.9</td>
<td>85.8</td>
</tr>
<tr>
<td>14</td>
<td>63.9</td>
<td>67.2</td>
<td>71.5</td>
<td>79.4</td>
<td>84.6</td>
<td>62.6</td>
<td>65.4</td>
<td>70.6</td>
<td>78.3</td>
<td>88.8</td>
</tr>
<tr>
<td>15</td>
<td>65.6</td>
<td>69.1</td>
<td>73.5</td>
<td>81.9</td>
<td>88.0</td>
<td>64.2</td>
<td>67.1</td>
<td>72.6</td>
<td>80.7</td>
<td>91.9</td>
</tr>
<tr>
<td>16</td>
<td>67.4</td>
<td>70.9</td>
<td>75.6</td>
<td>84.5</td>
<td>90.4</td>
<td>65.7</td>
<td>68.8</td>
<td>74.6</td>
<td>83.1</td>
<td>94.9</td>
</tr>
<tr>
<td>17</td>
<td>69.1</td>
<td>72.8</td>
<td>77.6</td>
<td>87.0</td>
<td>91.8</td>
<td>67.3</td>
<td>70.5</td>
<td>76.8</td>
<td>85.6</td>
<td>96.0</td>
</tr>
<tr>
<td>18</td>
<td>70.8</td>
<td>74.6</td>
<td>79.6</td>
<td>89.6</td>
<td>95.2</td>
<td>68.9</td>
<td>72.2</td>
<td>78.6</td>
<td>87.9</td>
<td>101.0</td>
</tr>
</tbody>
</table>
Metabolic Syndrome Criteria

• Hypertension:
  • It may look ok but you need to compare it to the percentiles based on age.
  • >90th percentile is HTN.

• [Link](http://www.nhlbi.nih.gov/guidelines/hypertension/child_tbl.pdf)
  • Repeat with a manual cuff!
  • Monitor B/P’s at school by nurse for 2 weeks.
  • Refer to nephrology hypertension clinic for diagnosis and follow.
Metabolic Syndrome Criteria

• Dyslipidemia
  • HDL cholesterol ≤ 40 mg/dl. (Happy Cholesterol).
  • Triglycerides ≥ 110mg/dl.

• Very common in children with metabolic syndrome.
• Treat low HDL by increasing exercise.
• Treat high triglycerides with diet. Get rid of the concentrated sugars!
• Treat high TG non-responsive to diet changes with Omega 3 Fatty Acids 1 gm BID.
Metabolic Syndrome Criteria

- **Impaired Fasting Glucose**: Glucose ≥ 100 mg/dl
- **Impaired Glucose Tolerance**: Glucose ≥ 140 mg/dl two hours after 75 gm glucose challenge.
- **Type-2 Diabetes**: Two fasting glucose results ≥ 126 mg/dl. Or a two hour glucose level after challenge ≥ 200 mg/dl. A random glucose of ≥ 200 mg/dl. [HbA1c of ≥ 6.5%—should be verified by oral glucose tolerance test (gold standard)].

Metabolic Syndrome—Labs?

- HbA1c, BMP, Liver Function, Lipid panel, thyroid studies if there is a family history.

- Do not diagnose a child with impaired glucose tolerance or type-2 diabetes solely based on the HbA1c (unless of course it is obvious). The gold standard is an oral glucose tolerance test with a 75 gm glucose challenge.
Treatment

• Lifestyle Education, Diet, Exercise………ad nauseam.

• Refer to a nutritionist.

• Refer to weight management.

• Exercise
Treatment

• Oral glucose tolerance test before starting metformin treatment. Need to know what you are treating.

• Plain metformin works better than metformin ER.

• Start metformin 500mg once a day with food for one week and then increase to BID. If not tolerating try one half a tablet for a week and increase from there or change to extended release formulation.

• If impaired glucose or type 2 diabetes increase as tolerated to 1000mg twice daily or 2000mg daily of the extended release formulation.
“Sorry the chocolates are opened. My blood sugar got too low on the way here.”
Polycystic Ovarian Syndrome (PCOS)

• “PCOS is the most common endocrine disorder, affecting women of reproductive age” (Hardy & Norman, 2013, p. 751).

• Prevalence of 11.9% of women of reproductive age using the Rotterdam Criteria (Hardy & Norman, 2013).

• Many common signs and symptoms of PCOS in adolescents overlap with normal puberty leading to over and under diagnosis (Hardy & Norman, 2013).

• Hyperandrogenism is fundamental to the presentation of PCOS in female adolescents (Legro et al., 2013).
Polycystic Ovarian Syndrome

• Signs and Symptoms:
  • Irregular menstrual periods which means “not every month”
  • Cycles that are very heavy or very light
  • Unwanted hair growth on the face and neck, chest, back, hands, or around the nipples
  • Acne
  • Thinner hair (male pattern baldness)
  • Acanthosis nigricans
  • Weight problems usually but not always
Anovulatory Dysfunction

- Typical post menarcheal cycle is 28 days with a range of 24-35 days, but may take a year or more to regulate (Hardy & Norman, 2013).

- Difficult to delineate which cycles are immediate post-menarcheal due to immaturity and which are ongoing ovulatory dysfunction (Hardy & Norman, 2013).
Diagnosis—Rotterdam Criteria

• Include two of the following in addition to exclusion of related disorders:
  • Oligo or anovulation
  • Clinical and or biochemical signs of hyperandrogenism
  • Polycystic ovaries (Legro et al., 2013).
  • Definition: “At least 12 follicles measuring 2–9 mm in diameter and increased ovarian volume greater than 10 ml” (Rackow, 2012).

The best ultrasound imaging of the ovaries is trans-vaginally or trans-rectally which are both inappropriate in an adolescent (Williams, Ong, & Dunger, 2013).

Ultrasound is of limited value in adolescents as ovarian morphology changes over time; Interpret with caution (Hardy & Norman, 2013).
Polycystic Ovarian Syndrome

• Clinical presentation of adolescents:
  • Overweight or obese (Higher risk due to normal insulin resistance related to puberty). Forty-three percent in a recent study (Flannery et al., 2013).
  • Oligomenorrheoea
  • Secondary amenorrhoea
  • Hirsutism (60% of adolescents)
  • Acne

(Legro et al., 2013; Williams, Ong, & Dunger, 2013)
Polycystic Ovarian Syndrome - Labs?

- BMP, HbA1c, Liver function, Lipid panel (like Insulin resistance).
- Adrenal hormones: DHEAS, Androstenedione,
- 17-OHP (progesterone) to R/O CAH.
- Gonadotropins: LH, FSH, Estradiol (looking for ovarian failure).
- Prolactin (R/O prolactinoma).
- Ovarian overproduction of male hormone (Free testosterone, testosterone).
- HCG to R/O pregnancy.
- TSH, FT4

(Flannery et al., 2013; (Rahmanpour, Jamal, Mousavinasab, Esmailzadeh, & Azarkhish, 2012).
PCOS, Obesity, IR, IGT, DM2 & MS

• Increased adiposity associated with hyperandrogenism and increased metabolic risk. Recommendation to screen all adolescents with PCOS with BMI calculation and waist circumference (Legro et al., 2013).

• Menstrual abnormalities are associated with the onset of excess weight leading to increase risk of metabolic syndrome, IR, IGT, DM2, & dyslipidemia (high triglycerides, low HDL) (Legro et al., 2013).
Treatment

• Lifestyle changes!!! (Auble, Elder, Gross, & Hillman, 2013; Legro et al., 2013; Rackow, 2012).

• Metformin (treatment of choice if obese and seen in endocrinology) (Auble, Elder, Gross, & Hillman, 2013). However, in the clinical practice guideline—suggest use for PCOS with DM2, and IGT after lifestyle changes fail (Legro et al., 2013).

• Hormonal contraceptives (treatment of choice in adolescent medicine or pediatric gynecology) (Auble, Elder, Gross, & Hillman, 2013). First line treatment for adolescents with PCOS, lifestyle changes first line if overweight or obese, and metformin for IGT/metabolic syndrome or DM2 (Legro et al., 2013).
Good Resources Related to PCOS

- Find a registered dietitian (Academy of Nutrition and Dietetics): [www.eatright.org/programs/rdfinder/](http://www.eatright.org/programs/rdfinder/)
Questions?

Sally and Berta

The only photo of Millie not bouncing.
References


References

• Finkelstein, E. A. et al. (2012). Obesity and severe obesity forecasts through 2030. American Journal of Preventative Medicine, 42(6), 563-570.


References


