Nature and Nurture: Navigating Risk and Treatment for Type II Diabetes and Hyperinsulinemia

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Progress in Pediatrics
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Disclosures

• I have no relevant financial relationships with the manufacturers(s) of any commercial products(s) and/or provider of commercial services discussed in this CME activity

• I will review literature for use of metformin in obese children
Objectives

• Familiarize yourself with screening for type II diabetes and metabolic syndrome in obese and overweight patient as well as the general population
• Understand the indications for metformin and endocrine referral for children with hyperinsulinemia and type II diabetes
• Appreciate the importance of and tools for motivational interviewing in obese and overweight patients

Frontline of an Epidemic

• Prevalence
• Complications
• Risk factors
• Evaluation
• Management
Age-Adjusted Prevalence of Obesity and Diagnosed Diabetes Among US Adults

2010

Obesity (BMI≥30 kg/m²)  Diabetes

- Missing Data
- <14.0%
- 14.0%–17.9%
- 18.0%–21.9%
- ≥22.0%

- Missing Data
- <4.5%
- 4.5%–6.9%
- 7.5%–8.9%
- ≥9.0%


2011

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Prevalence of Diagnosed Diabetes, US

Historical Data: CDC DDT and NCCDPHP, (Change in measurement in 1996).
Hope

“Every new insight into Type 2 diabetes... makes clear that it can be avoided--and that the earlier you intervene the better. The real question is whether we as a society are up to the challenge... Comprehensive prevention programs aren’t cheap, but the cost of doing nothing is far greater...”

Gorman C. Why so many of us are getting diabetes: never have doctors known so much about how to prevent or control this disease, yet the epidemic keeps on raging, how you can protect yourself. Time 2003 December 8. Accessed at http://www.time.com/time/covers/1101031208/story.html.

Complications of Obesity

• Metabolic Syndrome
• Non-alcoholic fatty liver disease (NAFLD)
• Dyslipidemia
• Insulin Resistance/ Prediabetes
• Diabetes
Metabolic syndrome

- Developed by National Cholesterol Education Program Adult Treatment Panel III
- 3 of 5 risk factors predict diabetes and CVD
  - Hyperglycemia
  - Increased central adiposity
  - Elevated triglycerides
  - Decreased HDL
  - Elevated blood pressure
- Less defined in pediatrics

Schematic of metabolic syndrome
Dyslipidemia

- Increased insulin $\Rightarrow$ hepatic lipogenesis $\Rightarrow$ Release of free fatty acids and triglycerides $\Rightarrow$ further fat deposition

NAFLD

- Adipose cell hypertrophy $\Rightarrow$ insulin resistance $\Rightarrow$ impairs lipolysis suppression $\Rightarrow$ preference to visceral fat including locations such as liver $\Rightarrow$ cytokine release $\Rightarrow$ increased inflammation and ROS
Prediabetes

- Fasting glucose 100-125 mg/dL
- 140-175 mg/dL after glucose tolerance test
- HbA1c 5.7-6.4
- 5-10% progression to diabetes annually

Risk factors

- (1) first- or second-degree relative with T2DM,
- (2) minority race/ethnicity,
- (3) signs of insulin resistance (acanthosis nigricans) or comorbidities (hypertension, dyslipidemia, polycystic ovarian syndrome)
- (4) mother with diabetes or gestational diabetes during child’s gestation.

Aditi Khokhar MBBS, Vatcharapan Umpaichitra MD, Vivian L. Chin MD and Sheila Perez-Colon MD
Pediatric Clinics of North America, “Metformin Use in Children and Adolescents.” 2017-12-01, Volume 64, Issue 6, Pages 1341-1353,
### TABLE 5: Findings on Review of Systems in Obesity Assessment and Possible Causes

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Possible Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anxiety, school avoidance, social isolation</td>
<td>Depression</td>
</tr>
<tr>
<td>Severe incontinence</td>
<td>Pseudomembranous</td>
</tr>
<tr>
<td>Headaches</td>
<td>Asthma, lack of physical conditioning</td>
</tr>
<tr>
<td>Shortness of breath, sweating</td>
<td>Obstructive sleep apnea, obesity/hypertension</td>
</tr>
<tr>
<td>Sleep apnea, daytime sleepiness</td>
<td>Obstructive sleep apnea, obesity/hypertension</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>Gastroesophageal reflux disease, constipation</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>Gastroesophageal reflux disease, constipation, inflammatory bowel disease, IBD</td>
</tr>
<tr>
<td>Hip pain, lower leg, walking pain</td>
<td>Slipped capital femoral epiphysis, muscle weakness from weight (may be barrier to physical activity)</td>
</tr>
<tr>
<td>Fever</td>
<td>Generalized musculoskeletal pain (may be barrier to physical activity)</td>
</tr>
<tr>
<td>Weakness in muscles (&lt;70 yrs)</td>
<td>Polyscythisy syndrome, may be normal in nonobese males, Pseudo-Weil syndrome</td>
</tr>
<tr>
<td>Primary amenorrhea</td>
<td>Polyscythisy syndrome, Pseudo-Weil syndrome</td>
</tr>
<tr>
<td>Polyuria, polydipsia</td>
<td>Type 2 diabetes mellitus</td>
</tr>
<tr>
<td>Unexpected weight loss</td>
<td>Type 2 diabetes mellitus</td>
</tr>
<tr>
<td>Nocturnal enuresis</td>
<td>Obstructive sleep apnea</td>
</tr>
<tr>
<td>Endocrine</td>
<td>Increased cardiac risk, may be used as form of weight control</td>
</tr>
</tbody>
</table>

* These conditions are due to obesity.

### TABLE 6: Physical Examination Findings in Obesity Assessment and Possible Causes

<table>
<thead>
<tr>
<th>System</th>
<th>Findings</th>
<th>Possible Explanations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anthropometric</td>
<td>High BMI or waist circumference</td>
<td>Overweight or obesity, underlying endocrine or genetic condition</td>
</tr>
<tr>
<td>Waist signs</td>
<td>Elevated blood pressure</td>
<td>Hypertension, polycythemia, obesity, hypertension-related increase in blood pressure</td>
</tr>
<tr>
<td>Skin</td>
<td>Acanthosis nigricans</td>
<td>Common in black children, increased risk of skin resistance (diabetes)</td>
</tr>
<tr>
<td>Eyes</td>
<td>Papilledema, ptosis, VI paralysis</td>
<td>Pseudotumor cerebellum, increased intracranial pressure</td>
</tr>
<tr>
<td>Feet</td>
<td>Transfer hyper trophy</td>
<td>Obstructive sleep apnea, obesity</td>
</tr>
<tr>
<td>Neck</td>
<td>Goiter</td>
<td>Hypothyroidism</td>
</tr>
<tr>
<td>Chest</td>
<td>Wheezing</td>
<td>Asthma (may exacerbate or contribute to exercise intolerance)</td>
</tr>
<tr>
<td>Abdomens</td>
<td>Tenderness</td>
<td>Gastroenteritis, inflammatory bowel disease, NASH*</td>
</tr>
<tr>
<td>Reproductive system</td>
<td>Hepatomegaly</td>
<td>NASH*</td>
</tr>
<tr>
<td>Tanner stage</td>
<td>Prematurity obesity in &lt;15-yr-old white girls, &lt;15-yr-old black girls, &lt;10-yr-old boys</td>
<td></td>
</tr>
<tr>
<td>Abdominal crunch</td>
<td>Obstructive ascites</td>
<td>May be normal or due to increased fat</td>
</tr>
<tr>
<td>Upper extremities</td>
<td>Abnormal gait, limited range of motion</td>
<td>Slipped capital femoral epiphysis, osteoarthritis, polycythemia</td>
</tr>
<tr>
<td>Shoulder</td>
<td>Small bones and joints, polyarthry</td>
<td>Same-granola syndromes</td>
</tr>
</tbody>
</table>

* These conditions are due to obesity.
Management

- Dietary & Physical Activity Counseling
- Lab/ Comorbidities screening
- Pharmacotherapy including metformin
- Endocrine/ Surgery referral
Counseling

- Healthy food choices
- Exercise
- Sedentary activity
- Sleep hygiene
- Evaluate psychologic comorbidities

Examples

- portion control education
- reduced saturated dietary fat intake for children and adolescents >2 years of age
- US Department of Agriculture recommended intake of dietary fiber, fruits, and vegetables
- timely, regular meals, and avoiding constant "grazing" during the day, especially after school and after supper
- recognizing eating cues in the child’s or adolescent’s environment, such as boredom, stress, loneliness, or screen time
- encouraging single portion packaging and improved food labeling for easier use by consumers. (Ungraded Good Practice Statement)

- decreased consumption of fast foods
- decreased consumption of added table sugar and elimination of sugar-sweetened beverages
- decreased consumption of high-fructose corn syrup and improved labeling of foods containing high-fructose corn syrup
- decreased consumption of high-fat, high-sodium, or processed foods
- consumption of whole fruit rather than fruit juices
Approach

- Targeted
- Written
- Achievable
- Family-Engaged
- Patient-Centered
- Success-focused
Does metformin prevent/ delay onset of type II diabetes in children with obesity or insulin resistance?

Metformin

- For obese, non-diabetic patients, improvement in
  - Fasting glucose
  - Insulin level
  - BMI
  - Cholesterol
  - Blood pressure
- Small studies with conflicting magnitude of effect
- Meta-analysis (McDonagh) confirms small, short-term benefit for BMI
<table>
<thead>
<tr>
<th>Study</th>
<th>Inclusion Criteria</th>
<th>Age (yr)</th>
<th>Design/Description</th>
<th>Therapy</th>
<th>Major Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haffner et al. (2009)</td>
<td>Metformin dosage ≤ 1 g/day, metabolic syndrome, and at least 5 years of follow-up</td>
<td>40-60</td>
<td>RCT</td>
<td>Metformin 1.0 g twice daily vs placebo. The benefit was seen with lifestyle modification.</td>
<td></td>
</tr>
<tr>
<td>Sesti et al. (2006)</td>
<td>Fasting plasma glucose &lt; 10 mmol/L, BMI &lt; 30, normal OGTT</td>
<td>45-55</td>
<td>RCT</td>
<td>Metformin 1.0 g twice daily vs placebo. The benefit was seen with lifestyle modification.</td>
<td></td>
</tr>
<tr>
<td>Schnip et al. (2003)</td>
<td>BMI ≥ 30 kg/m², metabolic syndrome, and at least 3 years of follow-up</td>
<td>45-60</td>
<td>RCT</td>
<td>Metformin 1.0 g twice daily vs placebo. The benefit was seen with lifestyle modification.</td>
<td></td>
</tr>
<tr>
<td>Crock et al. (2003)</td>
<td>Metformin 1.0 g twice daily in the presence of prediabetes</td>
<td>45-55</td>
<td>RCT</td>
<td>Metformin 1.0 g twice daily vs placebo. The benefit was seen with lifestyle modification.</td>
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</tr>
<tr>
<td>Harper et al. (2002)</td>
<td>Metformin 1.0 g twice daily in the presence of prediabetes</td>
<td>45-55</td>
<td>RCT</td>
<td>Metformin 1.0 g twice daily vs placebo. The benefit was seen with lifestyle modification.</td>
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<tr>
<td>Kuwabara et al. (2001)</td>
<td>Metformin 1.0 g twice daily in the presence of prediabetes</td>
<td>45-55</td>
<td>RCT</td>
<td>Metformin 1.0 g twice daily vs placebo. The benefit was seen with lifestyle modification.</td>
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<tr>
<td>Dieter et al. (2000)</td>
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Pediatric Clinics of North America, “Metformin Use in Children and Adolescents.” 2017-12-01, Volume 64, Issue 6, Pages 1341-1353,
• 42 participants
• Case-Control Design
• Outcome: BMI-z and Insulin Resistance
• Conclusion: Metformin provided short-term improvements but findings weren’t sustained at 18 months

• 151 obese children in RCT
• Randomized to metformin & placebo
• BMI change for 3 & 6 months
• BUT fasting glucose, ALT, and adiponectin/leptin for 3 months but not 6 months
Marginal Gains in Physically Active Individuals
Adult “No Leisure Time Physical Activity” (BRFSS)

Metformin side effects

- Abdominal pain
- Nausea
- Bloating
- Diarrhea
- Metallic taste
- Lactic acidosis
Metformin

- Endocrine Society recommends against metformin in management of obesity BUT
- Consider in patient with
  - Obesity
  - Co-morbidities
  - Engagement
- Evaluate response

Increasing Sedentary Activity
*Hours per Week Watching TV, Internet, Video (Media Industry Report)*

From "Understanding Obesity Dynamics", A Foundation for Directing Change and Charting Progress. CDC. 2005
Some Sources of Complexity for Obesity

Multiple Goals
- Improve diet
- Increase physical activity
- Decrease physical inactivity
- Assure healthful conditions in diverse behavioral settings (i.e., home, school, work, community)
- Harness synergies with other social values (i.e., school performance, economic productivity, environmental protection)

Barriers
- Cost of caring for weight-related diseases
- Cost of health protection efforts
- Spiral of unhealthy habits leading to poor health leading to even less healthy habits
- Social reinforcement of diet and activity based on observing parents’, peers’, and others’ behavior
- Demand for unhealthy food and inactive habits stimulates supply
- Resistance by defenders of the status quo

Simultaneous Program Strategies
- Deliver healthcare services
- Enhance media messages
- Expand options in behavioral settings
- Modify trends in the wider environment (i.e., economy, technology, laws)
- Address other health conditions that impede healthy diet and activity (e.g., asthma, oral health, etc.)

Time Delays
- 1-2 year lag for metabolism to stabilize after change in net caloric intake
- 14 year lag for youth to age into adulthood
- 58 year lag for cohorts of adults
- Several years for programs to mature and for policies to be fully enacted/enforced
- At least several years to see policy impacts, and even longer to affect the wider environment

Complexity is Real... and Consequential

Referral

**Endocrinology**
- Criteria for diabetes
- Hypothyroidism

**Bariatric Surgery**
- Tanner IV or V, BMI >40 or 35 w/ comorbidities
- Refractory to compliance with stage III intervention
- Absence of psychologic impairment
- Adherence to dietary regimen
- Access to bariatric team

Bibliography

- Aditi Khokhar MBBS, Vatcharapan Umpaichitra MD, Vivian L. Chin MD and Sheila Perez-Colon MD. Pediatric Clinics of North America, “Metformin Use in Children and Adolescents.” 2017-12-01, Volume 64, Issue 6, Pages 1341-1353,