Metabolic complications of obesity in children

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Disclosures

- I have no actual or potential conflict of interest in relation to this program/presentation
Objectives

1. Identify potential metabolic complications in the evaluation of an obese pediatric patient

2. Know when to refer an obese pediatric patient to the pediatric subspecialist
Outline

• Case presentation
• Review the diagnostic criteria for overweight/obesity and health implications.
• Review obesity checklist
• Discuss screening for metabolic complications of obesity, treatment options and when to refer.
• Discuss the common referrals to the pediatric endocrinology clinic
15 year old male referred to the pediatric endocrinology office for evaluation of obesity and abnormal lab values. He has gym once a week, and plays video games 2+ hours a day.

FH of T2DM, MI.

Weight = 130 kg and BMI 38.8 kg/m2. Normal BP. Acanthosis nigricans neck, axillae. Tanner V.

Recent labs significant for random glucose 88 mg/dL, HgbA1c = 6.8%, HDL = 34, ALT = 183, AST = 102.
Body mass index (BMI) = \( \frac{\text{Weight (kg)}}{\text{Height (cm)} \times \text{Height (cm)}} \)

< 5^{th} \text{%ile} = \text{Underweight}

5-84^{th} \text{%ile} = \text{Normal weight range}

85-94^{th} \text{%ile} = \text{Overweight}

\geq 95^{th} \text{%ile} = \text{Obese}
Trends in the prevalence of obesity among US children and adolescents by age and survey year (National Health and Nutrition Examination Survey)

Data derived from *Health, United States, 2010: With Special Feature on Death and Dying*. NCHS, 2011.
Prevalence of obesity

Figure 2. Prevalence of obesity among children and adolescents aged 2–19, by sex and age: United States, 2009–2010

<table>
<thead>
<tr>
<th>Age in years:</th>
<th>2–19</th>
<th>2–5</th>
<th>6–11</th>
<th>12–19</th>
</tr>
</thead>
<tbody>
<tr>
<td>All¹</td>
<td>16.9</td>
<td>12.1</td>
<td>18.0</td>
<td>18.4</td>
</tr>
<tr>
<td>Boys</td>
<td>18.6</td>
<td>14.4</td>
<td>20.1</td>
<td>19.6</td>
</tr>
<tr>
<td>Girls¹</td>
<td>15.0</td>
<td>9.6</td>
<td>15.7</td>
<td>17.1</td>
</tr>
</tbody>
</table>

¹Significant increasing linear trend by age (p < 0.005).

Importance

Metabolic Syndrome

- A cluster of anthropometric, physiological and biochemical abnormalities that predict both type 2 diabetes mellitus and premature coronary artery disease
- Age-specific cutoffs for triglycerides, HDL, glucose, BP and waist circumference.
## Definitions of metabolic syndrome in children and adolescents

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Modified ATP III</th>
<th>IDF (10 to 16 years)</th>
<th>NHANES III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Required</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Waist circumference</td>
<td></td>
<td>≥90th percentile*</td>
<td>≥90th percentile</td>
</tr>
<tr>
<td>Number of abnormalities</td>
<td>≥3</td>
<td>≥2</td>
<td>All</td>
</tr>
<tr>
<td>Triglyceride</td>
<td>&gt;95th percentile</td>
<td>≥150 mg/dL (1.7 mmol/L)</td>
<td>≥110 mg/dL (1.24 mmol/L)</td>
</tr>
<tr>
<td>HDL</td>
<td>&lt;5th percentile</td>
<td>&lt;40 mg/dL (1.03 mmol/L)</td>
<td>≤40 mg/dL (1.03 mmol/L)</td>
</tr>
<tr>
<td>BP</td>
<td>Either</td>
<td>Either</td>
<td>≥90th percentile</td>
</tr>
<tr>
<td>Systolic</td>
<td>&gt;95th percentile</td>
<td>&gt;130 mmHg</td>
<td></td>
</tr>
<tr>
<td>Diastolic</td>
<td>&gt;95th percentile</td>
<td>≥85 mmHg</td>
<td></td>
</tr>
<tr>
<td>Glucose</td>
<td>Impaired glucose tolerance</td>
<td>≥100 mg/dL (5.6 mmol/L)</td>
<td>Fasting ≥110 mg/dL (6.1 mmol/L)</td>
</tr>
</tbody>
</table>

ATP III: Adult Treatment Panel; IDF: International Diabetes Federation; NHANES: National Health and Nutrition Examination Survey; HDL: high-density lipoprotein; BP: blood pressure.
Importance: CVD in adulthood

Cardiovascular Risk in Young Finns Study
2,200 adults initially studied at 3-18 y

- correlates of adult Carotid IMT = childhood BMI, LDL, SBP and smoking
- greater effect in pubertal than pre-pubertal ages
- increased CIMT persisted in adulthood if the child had high BMI during adolescence, independent of adult BMI

Raitakari OT, JAMA, 2003
Bogalusa Heart Study

Table 3. Odds Ratios of Risk Factors for Carotid IMT in Young Adults in the Upper Quartile vs Lower 3 Quartiles*

<table>
<thead>
<tr>
<th></th>
<th>Odds Ratio (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Body Mass Index</td>
</tr>
<tr>
<td>Childhood (4-17 y)</td>
<td>1.25 (1.01-1.54)</td>
</tr>
<tr>
<td>Adulthood (25-37 y)</td>
<td>1.09 (0.86-1.39)</td>
</tr>
<tr>
<td>Long-term cumulative risk (AUC)</td>
<td>1.16 (0.92-1.46)</td>
</tr>
</tbody>
</table>

Abbreviations: AUC, area under the curve from childhood to adulthood divided by follow-up years; HDL-C, high-density lipoprotein cholesterol; IMT, intima-media thickness; LDL-C, low-density lipoprotein cholesterol.

*Scores specific for age, race, and sex were used for carotid IMT and risk factors.

High childhood BMI and LDL correlated with Carotid IMT in adults aged 25-37

Li S, JAMA, 2003
Medical assessment of the overweight/obese child

Take a focused family history

- Obesity
  - 1 obese parent = 3 X risk
  - 2 obese parents = 13 X risk
- Type 2 diabetes mellitus
- Cardiovascular disease (hypertension, dyslipidemia)
- Early deaths from heart disease or stroke

Expert Committee Recommendations on the Assessment, Prevention and Treatment of Child and Adolescent Overweight and Obesity - 2007
Medical Assessment:
Perform a thorough review of systems

<table>
<thead>
<tr>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anxiety, school avoidance, social isolation (Depression)</td>
</tr>
<tr>
<td>Polyuria, polydipsia, weight loss (Type 2 diabetes mellitus)</td>
</tr>
<tr>
<td>Headaches (Pseudotumor cerebri)</td>
</tr>
<tr>
<td>Night breathing difficulties (Sleep apnea, hypoventilation syndrome, asthma)</td>
</tr>
<tr>
<td>Daytime sleepiness (Sleep apnea, hypoventilation syndrome, depression)</td>
</tr>
<tr>
<td>Abdominal pain (Gastroesophageal reflux, Gall bladder disease, Constipation)</td>
</tr>
<tr>
<td>Hip or knee pain (Slipped capital femoral epiphysis)</td>
</tr>
<tr>
<td>Oligomenorrhea or amenorrhea (Polycystic ovary syndrome)</td>
</tr>
</tbody>
</table>
Medical Assessment: Assess attitudes and behaviors

• Diet behaviors
  • Sweetened beverage consumption
  • Fruit and vegetable consumption
  • Frequency of eating out and family meals
  • Consumption of excessive portion sizes
  • Daily breakfast consumption

Expert Committee Recommendations on the Assessment, Prevention and Treatment of Child and Adolescent Overweight and Obesity - 2007
Medical Assessment: Assess attitudes and behaviors

- Physical Activity behaviors
  - Amount of moderate physical activity
  - Level of screen time and other sedentary activities
- Attitudes
  - Self-perception and concern about weight
- Readiness to change
- Successes, barriers and challenges

Expert Committee Recommendations on the Assessment, Prevention and Treatment of Child and Adolescent Overweight and Obesity - 2007
Medical Assessment: Perform a thorough physical exam

<table>
<thead>
<tr>
<th>Signs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poor linear growth (Hypothyroidism, Cushing’s, Prader-Willi syndrome)</td>
</tr>
<tr>
<td>Dysmorphic features (Genetic disorders, including Prader–Willi syndrome)</td>
</tr>
<tr>
<td>Acanthosis nigricans (NIDDM, insulin resistance)</td>
</tr>
<tr>
<td>Hirsutism and Excessive Acne (Polycystic ovary syndrome)</td>
</tr>
<tr>
<td>Violaceous striae (Cushing’s syndrome)</td>
</tr>
<tr>
<td>Papilledema, cranial nerve VI paralysis (Pseudotumor cerebri)</td>
</tr>
<tr>
<td>Tonsillar hypertrophy (Sleep apnea)</td>
</tr>
<tr>
<td>Abdominal tenderness (Gall bladder disease, GERD, NAFLD)</td>
</tr>
<tr>
<td>Hepatomegaly (Nonalcoholic fatty liver disease (NAFLD))</td>
</tr>
<tr>
<td>Undescended testicle (Prader-Willi syndrome)</td>
</tr>
<tr>
<td>Limited hip range of motion (Slipped capital femoral epiphysis)</td>
</tr>
<tr>
<td>Lower leg bowing (Blount’s disease)</td>
</tr>
</tbody>
</table>
Common Endocrine Referrals

- Obesity
  - Rule out thyroid dysfunction
  - Rule out cortisol excess
  - Rule out genetic syndrome
- Abnormal menstrual cycles +/- hirsuitism
- Receiving atypical antipsychotic medication that increases appetite resulting in obesity
Normal linear growth in obesity
Cushing’s syndrome:

Height percentile falls as weight percentile rises
Striae

Cushing’s syndrome

Stretch marks due to rapid weight gain
Acanthosis nigricans

• Correlated with obesity
• Risk factor for T2DM
• Inform parents will not wash off – but will diminish with weight loss!
Obesity

Endocrine causes

- Hypothyroidism
  - May be associated with a goiter, decreased growth velocity
  - Rarely a cause for obesity
  - Measure TSH, free T4

- Cushing’s syndrome
  - Poor linear growth, violaceous striae, easy bruising, hypertension
  - Uncommon condition in children
  - Rarely a cause for obesity
Obesity
Endocrine causes

- Testing for endocrine disorders is unlikely to be useful unless the patient is short in relation to the family’s background or is showing a deceleration in height velocity.
Obesity

Genetic causes

- The more common genetic syndromes associated with obesity are also associated with neurodevelopmental abnormalities (i.e. Prader Willi Syndrome)
- Rare monogenic obesity syndromes involving leptin/melanocortin pathway
- Identification of genetic disorders that may provide an explanation of the individual’s overweight problem, offer prognostic implications, and spare the family from feelings of guilt that often occur when traditional weight loss interventions are unsuccessful.
BMI 85-94%ile without risk factors:
• fasting lipid profile

BMI 85-94%ile, age 10 yrs and older, with risk factors:
• fasting lipid profile and glucose, AST, ALT

BMI > 95%ile, age 10 yrs and older
• fasting lipid profile and glucose, AST, ALT, others prn

Expert Committee
Recommendations on the Assessment, Prevention and Treatment of Child and Adolescent Overweight and Obesity - 2007
Laboratory tests

- HgbA1c
- Perform OGTT prn based on symptoms or elevated HgbA1c
- Free testosterone prn symptoms
Type 2 DM

- Risk factors in children:
  - obesity, acanthosis nigricans, family history, puberty, race (Hispanic, Black, Pima Indian, Asian)
- Insulin resistance with relative insulin deficiency
- Lifestyle change is a major modifying factor in progression and treatment
Prediabetes broadly refers to an intermediate stage between completely normal glucose levels and the clinical entity of type 2 diabetes.

Liese AD et al. The burden of diabetes mellitus among US youth: prevalence estimates from the SEARCH for Diabetes in Youth Study. 2006 Pediatrics 118:1510-8
Stages of Type 2 Diabetes

Insulin sensitizers

Insulin sensitizers + insulin secretagogues

Insulin sensitizers + Insulin

β-Cell Function (%)

Years From Diagnosis

IGT
Postprandial Hyperglycemia
Type 2 Diabetes Phase I
Type 2 Diabetes Phase II
Type 2 Diabetes Phase III

Type 2 Diabetes Mellitus: Treatment strategies

- Decrease insulin resistance (weight loss, exercise, metformin, thiazolidinediones)
- Correct insulin deficiency (insulin)
- Stimulate insulin secretion (sulfonylureas, repaglinide, incretin mimetics)

- Increase hepatic/muscle glucose uptake (metformin)
- Decrease hepatic glucose production (metformin, DPP-IV inhibitors, amylin analogs)
- Reduce CHO absorption (alpha-glucosidase inhibitors)

**Only metformin (age 10 +) and insulin FDA approved treatment in children**
Metformin

Pros:
- Increases hepatic + muscle glucose uptake
- Decrease hepatic glucose output
- Some safety/efficacy data in children
- Good response rate
- No weight gain or modest weight loss
- May also be beneficial for PCOS

Cons:
- GI side effects (often transient)
- May lose effectiveness over time
- Risk of lactic acidosis
  - Impaired renal function
  - Impaired liver function


Pharmacotherapy

- **Metformin**
  - decreased BMI slightly but significantly in several studies
  - may be useful in combating the weight gain observed in children taking atypical psychotropic medications, e.g., clozapine, olanzapine, risperidone, quetiapine, aripiprazole, and valproate

Treatment: weight loss surgery

- Gastric bypass and adjustable banding occasionally used to tx severe obesity in adolescents.
- T2DM usually remits post-op in 90% (11 pts) -related to degree of wt loss
- In adults, frequency or remission may be inversely related to age at surgery, duration of DM and severity of disease.

T2DM treatment outcomes

- TODAY (Treatment Options for T2DM in Adolescents and Youth) study
- 699 youth (10-17 yo)
- T2DM < 2 yrs, overweight or obese
- Run in period: metformin alone & lifestyle counseling to achieve hgbA1c < 8%
- Randomly assigned to metformin alone, metformin + rosiglitazone, or metformin + intensive lifestyle intervention.

T2DM treatment outcomes: the TODAY study

- **Primary outcome** = tx failure
  - HgbA1c ≥ 8% X 6 months or insulin requirement
- **Outcomes after mean 3.8 yrs tx**
  - Metformin = 51.7% tx failure
  - Metformin + rosi = 38.6% tx failure
  - Metformin + lifestyle = 46.6%
  - Metformin + rosi significantly better than metformin alone
- **Overall 45.6% failed tx; median time to failure of 11.5 m.**
- **Weight outcome** in lifestyle group not different than metformin alone group (31.2% vs. 24.3% reached target wt loss).

Metabolic complication: Dyslipidemia

- Lipid abnormalities found in 12%-17% of overweight and obese children
- 2008 AAP guidelines recommend fasting lipid profile in children as young as 2 years of age with a positive family history of dyslipidemia or premature CVD
- Universal screening once between ages 9-11 yrs, and once again between 17-21 yrs
- Recommendations are controversial

Dyslipidemia treatment

- Primary treatment is healthy lifestyle
- High triglycerides – low CHO, refined carbs and sugars
- High LDL – low saturated (12-15 g/day), no trans fat, high fiber
- Low HDL – increase poly and mono unsaturated fat
Dyslipidemia treatment
NHLBI 2011

- Consider statin tx @ ≥ 10 yrs if no response to 6 mos lifestyle therapy
  - LDL ≥ 190 mg/dl or
  - LDL ≥ 160 mg/dl
    - FH early coronary disease OR
    - 2 or more moderate risk factors, OR
    - One high-level risk factor
  - LDL ≥ 130 mg/dl
    - 2 high level RF, OR
    - 1 high level and 2 moderate RF
Complication: Hypertension

- Use a cuff large enough to cover 80% of the upper arm
- Use NHLBI tables which are standardized to the child’s height percentile

Normal < 90th %ile
Pre-HTN ≥ 90 and <95th %ile
HTN ≥ 95th %ile X 3

<table>
<thead>
<tr>
<th>AGE</th>
<th>BOYS HEIGHT %</th>
<th>GIRLS HEIGHT %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>50% 90%</td>
<td>50% 90%</td>
</tr>
<tr>
<td>2 Yr</td>
<td>106/61 109/63</td>
<td>105/63 108/65</td>
</tr>
<tr>
<td>5 Yr</td>
<td>112/72 115/74</td>
<td>110/72 112/73</td>
</tr>
<tr>
<td>8 Yr</td>
<td>116/78 119/79</td>
<td>115/76 118/78</td>
</tr>
<tr>
<td>11 Yr</td>
<td>121/80 124/82</td>
<td>121/79 123/81</td>
</tr>
<tr>
<td>14 Yr</td>
<td>128/82 132/84</td>
<td>126/82 129/84</td>
</tr>
<tr>
<td>17 Yr</td>
<td>136/87 139/88</td>
<td>129/84 131/85</td>
</tr>
</tbody>
</table>

Pediatrics Vol. 114 No. 2 August 2004 pp. 555-576
Hypertension: treatment

- Non-pharmacologic
  - Weight reduction if obesity-related
  - Exercise
  - Modify diet, salt restriction
  - Avoid alcohol, smoking

- Pharmacologic: if BP $\geq$ 95th % after 4-6 mos., symptomatic or target organ damage
  - Thiazide diuretic
  - ACE inhibitor
  - Angiotensin-receptor blocker
  - Beta blockers
  - Calcium channel blockers
Metabolic complication: Fatty liver

- Detected by abdominal sonography
- Caused by insulin resistance and obesity
- Between 10% and 25% of obese children have NASH: elevated transaminases, primarily alanine aminotransferase (ALT)
- Typically benign clinical course
- May be associated with increasing fibrosis and, rarely, progression to cirrhosis and liver cancer

Alfire ME, Treem WR Nonalcoholic fatty liver disease. Pediatr Ann 2006
Metabolic complication: Fatty liver

- Weight loss is an effective treatment to reduce liver fat and transaminases.
- Weight loss of 7-10% linked with ~ 50% drop in liver fat levels
- Vitamin E 800 IU/day if bx proven NASH and no diabetes
- Pioglitazone
Metabolic complication: Hyperandrogenism

- Hyperandrogenism
  - associated with BMI ≥95th percentile and hyperinsulinism in pre- to mid-pubertal girls
  - free testosterone concentrations in such girls are higher than in girls with a BMI <85th percentile
  - place the obese adolescent girl at risk for polycystic ovary disease (PCOS) and menstrual irregularities

Hyperandrogenism: treatment

- Lifestyle change effective in treating symptoms
- Metformin successfully used to treat PCOS with and without concomitant obesity and insulin insensitivity (not FDA approved for this indication)
- OCP +/- spironolactone

Nutritional Counseling

- Motivational interviewing
- Avoid blame and criticism
- Express concern and empathy
- Discuss importance of family involvement
Nutritional Counseling

- Limit sugar-sweetened beverages
- Eat at least 5 servings of fruits and vegetables a day
- Limit eating out, especially at fast food
- Limit portion sizes
- Involvement of the parents and home setting promotes greater weight loss or maintenance

Expert Committee Recommendations on the Assessment, Prevention and Treatment of Child and Adolescent Overweight and Obesity – 2007
Physical Activity Counseling

- Moderate to vigorous physical activity for at least 60 minutes a day—increase gradually!
- Non-weight bearing activities if BMI ≥ 97%
- Decrease sedentary activities i.e. limit tv to 2 hours/day

Expert Committee Recommendations on the Assessment, Prevention and Treatment of Child and Adolescent Overweight and Obesity - 2007
Obesity referral plan

Refer to …

• geneticist if syndromic features are present
• psychiatrist or psychologist if mood disorder is suspected
• nephrologist if hypertension is present on three consecutive visits
Obesity referral plan

Refer to nutritionist

- Note that patient’s compliance with appointment is higher when they schedule the appointment themselves
- Patient/family should at least be in contemplative stage
Obesity referral plan

Refer to endocrinologist

- impaired fasting glucose or glucose intolerance
- hyperglycemia in the diabetic range
- polycystic ovarian syndrome
Case follow up: ZG

- Started metformin 500 mg once daily
- Liver ultrasound = fatty liver
- Parents and patient motivated by “diabetes scare”.
- Pt. exercising daily 30 - 60 mins/walking, decreased portions, reduced simple carbs (i.e. white bread, juice).
- 1 month follow up: Wt = 119.9 kg (loss of 10.1 kg), BMI = 36.6 kg/m2. HgbA1c = 5.4%, ALT = 79 IU/L, AST = 34 IU/L.