Obesity and Type 2 Diabetes in Youth:

How did we get here and what can we do about it?

April 27, 2019
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Conflict of Interest Disclosure
I have no conflicts of interest to disclose
I will be discussing off-label use of medications

Objectives
1. Review the prevalence and trends in pediatric obesity and type 2 diabetes
2. Discuss the causes and diagnosis of obesity and type 2 diabetes in youth
3. Learn about treatment options for obesity and type 2 diabetes in youth
Case

13 year old boy referred to you, by his primary care provider, for new onset diabetes

Case

Fam Hx: Mother is obese and had gestational diabetes; paternal grandparents have T2DM
Soc Hx: Mom estimates 4-5 hours per day on TV/video games/phone
PE: BMI 36 kg/m² (>99%)
BP 134/88 (>95%)
Dark skin on base of the neck and in the armpits
Questions to Consider

1. What are his risk factors?

2. Why is he gaining weight and how could that contribute to his T2DM risk?

3. How might you help him?

Prevalence and Trends in Obesity and Type 2 Diabetes in Youth

• 18.5% of all children and adolescents in US have obesity

• Severe Pediatric Obesity:
  • Fasting growing obesity category
  • 3.8 - 5.4 million children/adolescents in US
  • Greatest risk for developing obesity-related health consequences: T2D/CVD
  • Lifestyle modifications generally ineffective in this population

Freedman et al. / Pedi, 2007
Alarming Trend in Obesity

- Projected obesity trends¹
  - By 2030, additional 65 million adults with obesity in US
  - 6-8 million additional cases of DM
  - 5-7 million additional cases of heart disease/stroke
  - 500,000 additional cases of cancer
  - Associated additional cost: $48-66B a year

- The economic burden of obesity worldwide²
  - Global Cost:
    - 0.7-2.8% of total health care expenditures for obesity
    - 9.1% of total health care expenditures for overweight and obesity

Relation of Childhood BMI to Adult BMI

- Sinaiko et al, Circulation, 1999
  - BMI at mean age 7 vs BMI at mean age 24
  - r = 0.638
  - p = 0.0001

¹ Yang et al, Lancet, 2011
² Withrow and Alter, Obes Rev, 2011
Alarming Trend in Diabetes

- 30.3 million people in the US have diabetes (9.4% of population)\(^1\)
  - 23 million diagnosed, 7 million undiagnosed
  - 1.5 million new cases of T2D in adults per year
- Additional 84.1 million have prediabetes (34% of population)
- Overall risk of death twice that of people without diabetes of similar age
- Leading cause of blindness, ESRD, non-traumatic leg amputation
- 2-4x increased risk for cardiovascular disease
- 1 in 3 children born in the US in 2000 will develop diabetes (CDC)\(^2\)
  - 50% of African American and Latino children may develop T2DM
- Worldwide, 366 million people will have T2D by 2030\(^3\)

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3. Wild et al, Diabetes Care, 2004

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Rates of New Cases of Pediatric Type 2 Diabetes in US from 2002-2012

Rates increased by 7.1% annually\(^4\)
- 9 per 100,000 youth/year in 2002-2003
- 12.5 per 100,000 youth/year in 2011-2012

Higher incidence in Native American, non-Hispanic Blacks, Hispanics
T2D in youth from < 2% to 25% of new onset diabetes\(^5\)

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1. SEARCH study, NEJM, 2017
2. SEARCH Study, Pediatrics, 2006
Additional information about our patient

- Reports no symptoms of polyuria or polydipsia
- Laboratory tests provided by his doctor include (normal)
  - Fasting glucose of 167 (<100)
  - HbA1c is 7.5% (<5.7%)
  - Triglycerides 289 (<150)
  - HDL 28 (>40)
  - ALT (liver enzyme) 65 (<35)

Causes and Diagnoses of Obesity and Type 2 Diabetes in Youth

- Appetite/Safety
- Hormone Dysregulation
- Iatrogenesis
- Television
- Antioxidant Use
- Anxiety
- Sedentary Lifestyle
- Leptin Resistance
- Poverty
- Devices
- Adverse Life Experiences
- Elevators
- Appetite/Safety
- Hormone Dysregulation
- Iatrogenesis
- Television
- Antioxidant Use
- Anxiety
- Sedentary Lifestyle
- Leptin Resistance
- Poverty
- Devices
- Adverse Life Experiences
- Elevators

Distribution of Types of Food in TV Advertising Targeted to Children or Teens, 2005

Among all food ads targeted to children or teens, percent that are for:

- 34% Other
- 28% Fast Food
- 10% Snack Foods
- 5% Cereal
- 4% Meat
- 2% Produce
Popular Teen-Age Items....

• Chipotle
  - Chicken Burrito: rice, black beans, cheese, salsa, grilled chicken
  - 1154 calories

• Starbucks
  - Frappuccino (16 oz)
  - 430 Calories

• Popular Beverages (Pop, Monster Energy, etc.)
  - 20 oz: 260 calories

Recommended calorie target for weight loss in 13-18 y/o patients with type 2 diabetes: 1200-1500 kcal/day

Interactions among hormonal and neural pathways that regulate food intake and body-fat mass

Organs: large intestine, small intestine, stomach, adipose tissue, brain

Hypothalamic Involvement: PVN, LVH, NST, Arcuate nucleus of the accumbens

Hormones: leptin, ghrelin, PYY, NPY, GH, AgRP, GLP

Energy Balance and Steady State
Energy Balance and Steady State: Weight Regain

Risks of obesity increases with sedentary activity

Primary Factors Contributing to Development of T2DM in Children
Type 2 Diabetes is a continuum of progressive, pathologic changes in Insulin Supply, Secretion, and Demand.

Definitions: Pediatric Obesity

- Overweight: BMI ≥ 85th but < 95th for age and sex
- Obese: BMI ≥ 95th
- Severe Obesity: BMI ≥ 120% of the 95th percentile or BMI ≥ 35 mg/m²

Criteria for the Diagnosis of Pre-Diabetes

<table>
<thead>
<tr>
<th>Test</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting plasma glucose</td>
<td>≥ 100 mg/dl to &lt; 126 mg/dl</td>
</tr>
<tr>
<td></td>
<td>or</td>
</tr>
<tr>
<td>2-hour OGTT*</td>
<td>≥ 140 mg/dl to &lt; 200 mg/dl</td>
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<tr>
<td></td>
<td>or</td>
</tr>
<tr>
<td>Hemoglobin A1c</td>
<td>≥ 5.7% to &lt; 6.5%</td>
</tr>
</tbody>
</table>

* Using a glucose load containing the equivalent of 1.75 mg/kg (max 75 g) anhydrous glucose dissolved in water. Result should be confirmed by repeat testing.
Criteria for the Diagnosis of Diabetes

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<td>Fasting plasma glucose*</td>
<td>≥ 126 mg/dl</td>
</tr>
<tr>
<td>Casual glucose</td>
<td>≥ 200 mg/dl with symptoms</td>
</tr>
<tr>
<td>2-hour OGTT</td>
<td>≥ 200 mg/dl</td>
</tr>
<tr>
<td>Hemoglobin A1c</td>
<td>≥ 6.5%</td>
</tr>
</tbody>
</table>

*In the absence of unequivocal hyperglycemia, result should be confirmed by repeat testing.

Pediatric Type 2 DM: Presentation

- Asymptomatic
  - Insidious (no recognized symptoms)
- Symptomatic:
  - Polyuria, polydipsia, fatigue, blurry vision, possible weight loss (in the setting of baseline overweight)
  - Diabetic ketoacidosis (DKA)
  - Non-ketotic hyperosmolar coma
    - Characterized by shock, non-acidosis, stupor/coma
    - Fatality rates: “60 deaths/yr

Screening for Obesity and Type 2 Diabetes in Youth
Screening for Obesity

USPSTF Recommendation Statement

Clinical screening for obesity in children 6 years and older

Offer/refer to comprehensive, intensive behavioral interventions to promote improvements in weight status

Category B Recommendation

Screening for Type 2 Diabetes

- Could be considered in youth who are overweight (BMI ≥ 85%) or obese (BMI ≥ 95%) and who have 1+ risk factors
  - Maternal history of DM or GDM during the child's gestation
  - Race/ethnicity (Native American, African American, Latino, Asian American, Pacific Islander)
  - Signs or conditions associated with insulin resistance (acanthosis nigricans, hypertension, dyslipidemia, PCOS, or SGA birth weight)

*After onset of puberty or after 10 years old, whichever occurs earlier

If tests normal: repeat testing at a minimum of 3-year intervals or more frequently if BMI increasing

Acanthosis Nigricans: Sign of Insulin Resistance
What about Type 1 Antibody Testing?

- Children with overweight/obesity in whom T2D is considered should have pancreatic autoantibodies tested to exclude T1D
  - GAD65, IA2, insulin Ab, (Zinct8?)
- Genetic evaluation to exclude monogenic DM should be considered based on presentation and characteristics
  - 4.5-8% youth with clinical features suggestive of T2D have monogenic DM

Position Statement, Diabetes Care, 2018

Complications from Obesity and Type 2 Diabetes in Youth

Co-morbid Metabolic Conditions Highly Prevalent in Youth with T2DM

<table>
<thead>
<tr>
<th>TODAY Cohort (n = 704)</th>
<th>Co-morbidity</th>
<th>Present at Baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low HDL (♀&lt;50, ♂&lt;40)</td>
<td>80%</td>
<td></td>
</tr>
<tr>
<td>High TG (&gt; 200)</td>
<td>10%</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>14%</td>
<td></td>
</tr>
<tr>
<td>ALT 1.5-2.5 &gt; ULN (&gt;2.5 excluded)</td>
<td>3%</td>
<td></td>
</tr>
<tr>
<td>Microalbuminuria</td>
<td>13%</td>
<td></td>
</tr>
</tbody>
</table>

Copeland et al, JAMA, 2011
Increased Risk for Premature CVD in Youth with T2DM

- Other Evidence for Premature Cardiovascular Disease
  - Increased vascular stiffness
  - Higher aortic pulse wave pressure
  - Inflammatory cytokines

- Pediatric Criteria for Metabolic Syndrome (three of five)
  1. Fasting glucose ≥ 110 mg/dl
  2. Waist circumference ≥ 90th %
  3. Triglycerides ≥ 110 mg/dl
  4. HDL-C ≤ 40 mg/dl
  5. Blood pressure ≥ 90%

Atherosclerosis begins in Childhood

Youth with T2DM: More Rapid Decline in Beta Cell Function Compared to Adults
**Short and Long Term DM Complications**

**PEDIATRIC**
- Poor Growth and Delayed Puberty
- Depression
- Eating Disorders
- DKA
- Hypoglycemia
- Hyperlipidemia
- Nephropathy
  - Microalbuminuria

**ADULT**
- Nephropathy
- Retinopathy
  - Leading cause blindness
- Neuropathy
- CVD
- Early MI
- Limited Joint Mobility
- Skin Disorders
  - Necrobiosis Diabeticorum
  - Ulcers

**Management of Obesity and Type 2 Diabetes in Youth**

**Guidelines**

*Pediatric Obesity—Assessment, Treatment, and Prevention: An Endocrine Society Clinical Practice Guideline*

*American Diabetes Association. Evaluation and Management of Youth-Onset Type 2 Diabetes: A Position Statement by the American Diabetes Association*
Pediatric Obesity Treatment: General Principles

- Intensive, age-appropriate, culturally sensitive, family-centered lifestyle modification therapy
- Healthy eating habits
- Physical activity: minimum 20 minutes daily; goal 60 minutes
- Evaluate and treat psychosocial co-morbidities
- Consider pharmacotherapy
- Consider bariatric surgery

Styne et al, JCEM, 2017

Evidenced-Based Dietary Principles

- Decrease consumption of fast foods, added table sugar, high-fructose corn syrup
- Eliminate sugar-sweetened beverages
- Decrease consumption of high-fat, high-sodium, or processed foods
- Consume whole fruit rather than fruit juices
- Educate on Portion control
- Reduce saturated dietary fat intake (>2 years)
- Follow USDA intake of dietary fiber, fruits, and vegetables
- Timely, regular meals, and avoiding constant “grazing”
- Recognize eating cues (boredom, stress, loneliness, or screen time)
- Encourage single portion packaging and improved food labeling for easier use by consumers
  - Ungraded good practice statement

Styne et al, JCEM, 2017

Benefits of Juice

A glass full of nutrition

Protein, benefits of juice, meal plan, where to buy, our story, contact us, sign up, search, healthy, kids drinks, and what you love.

A Glass Full of Nutrition

A glass full of nutrition.
MISLEADING!!!

20 oz Tropicana:
290 calories
59 gm sugar

20 oz Coke:
240 calories
65 gm sugar
Evidence-Based Exercise Principles

- 60 minutes/day moderate to vigorous physical activity to reduce BMI and improve glycemic control
  - “Talk Test”
    - Moderate activity: can talk but not sing
    - Vigorous activity: cannot talk without pausing to catch a breath

- Provide written prescription to engage in physical activity, including a “dose” describing ideal duration, intensity, and frequency
  - May improve compliance

- 60 minutes do not have to be accomplished in 1 session

Facilitate the following:

- Ability to safely walk to/from school
- Increased use of stairs (improved signage to indicate their location)
- Increased breaks for movement in classroom
- Increased movement during recess/gym

Limit non-academic screen time to less than 2 hours per day

- US Department of Health (< 2 hours)
- American Academy of Pediatrics (< 2 hours)
- Endocrine Society (1-2 hours per day)
<table>
<thead>
<tr>
<th>Medication</th>
<th>Approved</th>
<th>MOA</th>
<th>Trial</th>
<th>Weight Loss Relative to Baseline Weight, Drug versus Placebo</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orlistat</td>
<td>1999</td>
<td>Gastrointestinal lipase inhibitor</td>
<td>XENDOS</td>
<td>-5.8 vs. -3.0 (yr)</td>
<td>Not reported</td>
</tr>
<tr>
<td>Lorcaserin</td>
<td>2012</td>
<td>Serotonin 2C Receptor Agonist</td>
<td>BUDDOM</td>
<td>-5.8 vs. -3.2 (yr)</td>
<td>-5.8 vs. -3.1 (yr)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>BUDDOM</td>
<td>-7.2 vs. -3.9 (yr)</td>
<td>-7.2 vs. -3.6 (yr)</td>
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<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>BUDDOM-DM</td>
<td>-4.7 vs. -3.6 (yr)</td>
<td>-4.5 vs. -3.5 (yr)</td>
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<tr>
<td>Phenetermine/Topiramate</td>
<td>2012</td>
<td>Sympathomimetic amine with anorectic effect/unknown</td>
<td>CONQUER</td>
<td>-6.3 vs. -4.1 (yr)</td>
<td>-6.3 vs. -4.0 (yr)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>EQUIP</td>
<td>Not reported</td>
<td>-0.1 vs. -3.3 (yr)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>SEQUEL</td>
<td>Not reported</td>
<td>-0.5 vs. -3.6 (yr)</td>
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<tr>
<td>Naltrexone/Bupropion</td>
<td>2014</td>
<td>Opioid receptor antagonist/antidepressant</td>
<td>COR-I</td>
<td>-6.1 vs. -4.1 (yr)</td>
<td>-6.1 vs. -3.9 (yr)</td>
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<td></td>
<td></td>
<td></td>
<td>COR-II</td>
<td>-6.2 vs. -3.1 (yr)</td>
<td>-6.4 vs. -3.2 (yr)</td>
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<tr>
<td></td>
<td></td>
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<td>COR-Diabetes</td>
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<tr>
<td>Liraglutide</td>
<td>2014</td>
<td>GLP-1 receptor agonist</td>
<td>SCALE Diabetes/Pre-DM</td>
<td>-8.4 vs. -2.8 (yr)</td>
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<td></td>
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<td>-6.0 vs. -2.1 (yr)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>SCALE Maintenance</td>
<td>-6.2 vs. -0.1 (yr)</td>
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**Mechanisms of Action**

**Orlistat**: Gastrointestinal lipase inhibitor  
**Lorcaserin**: Serotonin 2C receptor agonist  
**Phentermine/Topiramate**: Sympathomimetic amine with anorectic effect/mechanism unknown  
**Naltrexone/Bupropion**: Opioid receptor antagonist and aminoketone antidepressant  
**Liraglutide**: GLP-1 receptor agonist
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<td>XENDOS</td>
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<td>2012</td>
<td>Sympathomimetic amine with anorectic effect/ unknown</td>
<td>CONQUIX</td>
<td>-10.2 vs -5.4 (1 yr)</td>
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**Advanced Therapies for Pediatric Obesity**

**October 4, 2018**

University of Minnesota Masonic Children’s Hospital

**PRESENTED BY**

Center for Pediatric Obesity Medicine

**COORDINATING COMMITTEE:***

*Any changes or updates to this document must be approved by the Coordinating Committee.*

**PARTICIPANTS:***

*Participants must disclose any financial relationships with commercial interests that may have a direct or indirect influence on the content of this presentation.*

**CE CREDIT:***

*Credit will be awarded to participants who attend the entire program and complete the evaluation and post-test.*

**INTENDED AUDIENCE:***

*Health care providers, researchers, and others interested in the clinical management of pediatric obesity.*

**DISCLOSURES:***

*All presenters have disclosed any relevant financial relationships with commercial interests.*

**EDUCATIONAL OBJECTIVES:***

*After completing the activity, learners should be better able to:*

- Identify therapeutic strategies for pediatric obesity in a safe and responsible manner.
- Integrate pharmacologic interventions into their treatment plans.
- Recognize the mechanisms of action and side effects of currently FDA-approved and off-label medications for the treatment of obesity in adults and children.

**ADVANCED THERAPIES:***

*For advanced therapies, learners should be able to:*

- Use advanced therapies for pediatric obesity in a safe and responsible manner.
- Integrate advanced pharmacologic interventions into their treatment plans.
- Recognize the mechanisms of action and side effects of currently FDA-approved and off-label medications for the treatment of obesity in adults and children.
Type 2 Diabetes: Pharmacologic Management in Youth

- Metformin and/or insulin alone or in combination
- Initial treatment must account for fact that DM type often uncertain in first few weeks (may have DKA, etc.)
- Immediate therapy should address hyperglycemia and metabolic derangements
  - Can tailor when diagnosis established (antibodies, etc.)

ADA Consensus, 2018

Type 2 Diabetes: Initial Treatment in Youth

<table>
<thead>
<tr>
<th>A1c &lt; 8.5% (no acidosis or ketosis)</th>
<th>A1c ≥ 8.5% (no acidosis with or without ketosis)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lifestyle Modification</td>
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</tr>
<tr>
<td>Metformin PO BID (titrate to 2 gm)</td>
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</tr>
<tr>
<td>Check antibodies</td>
<td>Basal Insulin:</td>
</tr>
<tr>
<td></td>
<td>- Start 0.5 u/kg/day</td>
</tr>
<tr>
<td></td>
<td>- Titrate to glycemic control every 2-3 days</td>
</tr>
<tr>
<td></td>
<td>Check antibodies</td>
</tr>
</tbody>
</table>

If in DKA at initial presentation: treat and manage as type 1 DM (metformin can be added when acidosis resolved)

ADA Consensus, 2018

Type 2 Diabetes: Ongoing Management in Youth

- In youth initially started on insulin and metformin
  - If meeting glucose targets insulin can be tapered over 2-6 weeks by decreasing insulin dose 10-30% every few days
- If glycemic target not met with metformin alone or cannot tolerate metformin
  - Start basal insulin
- If metformin + basal insulin (up to 1.5 u/kg/day) ineffective
  - Assess compliance
  - May need higher dose basal insulin or to start bolus insulin

ADA Consensus, 2018
Type 2 Diabetes: Other Options in Youth

- ADA does not recommend any other options for youth < 18 years old because not enough studies done
- Does not mean that these medications are not used
- Need for more studies

### Class Examples, Mechanism of Action, Side Effects

<table>
<thead>
<tr>
<th>Class</th>
<th>Examples</th>
<th>Mechanism of Action</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biguanides</td>
<td>Metformin</td>
<td>↓ insulin resistance, hepatic glucose production; ↑ glucose uptake</td>
<td>GI, lactic acidosis</td>
</tr>
<tr>
<td>Sulfonlureas</td>
<td>Glibizide, Glipizide</td>
<td>Stimulates β-cell insulin secretion</td>
<td>Hypoglycemia, weight gain</td>
</tr>
<tr>
<td>Meglitinides</td>
<td>Repaglinide</td>
<td>Stimulates glucose-dependent secretion of insulin from β-cell</td>
<td></td>
</tr>
<tr>
<td>α-Glucosidase inhibitors</td>
<td>Acarbose</td>
<td>Delays glucose absorption by inhibiting complex sugar breakdown</td>
<td>GI</td>
</tr>
<tr>
<td>GLP-1 agonists</td>
<td>Exenatide, Liraglutide</td>
<td>Incretin effect; slows gastric emptying; improves β-cell function; ↓ appetite</td>
<td>Acute pancreatitis, GI; hypoglycemia, headaches, c-cell hyperplasia (MTC)</td>
</tr>
<tr>
<td>DPP-4 inhibitors</td>
<td>Saxagliptin, Sitagliptin</td>
<td>Inhibits DPP-4 enzyme</td>
<td>Acute pancreatitis, URI, UTI, nasopharyngitis, headaches, GI, hypoglycemia</td>
</tr>
<tr>
<td>Amylin analog</td>
<td>Exenatide, Liraglutide</td>
<td>Inhibits postprandial glucagon secretion; delays gastric emptying; improves satiety</td>
<td>Weight gain, edema, anemia, ↑ AST/ALT</td>
</tr>
<tr>
<td>Thiazolidinediones</td>
<td>Rosiglitazone, Pioglitazone</td>
<td>PPAR-γ inhibitor; ↑ insulin sensitivity, ↓ hepatic glucose output</td>
<td>Euglycemic ketoacidosis, UTI, Candida auris vaginitis</td>
</tr>
<tr>
<td>SGLT-2 inhibitors</td>
<td>Canagliflozin, Empagliflozin</td>
<td>Increases glucose secretion in urine</td>
<td></td>
</tr>
</tbody>
</table>

Back to our patient...

- Started metformin 500 mg daily; titrated to 1,000 mg twice a day
- Met with dietician about healthier eating habits
  - Eliminated sugar-sweetened beverages
  - Packs lunch from home
- Realizes he likes playing basketball; starts playing with kids from the neighborhood twice after school and on both weekend days
- Cuts Xbox and TV time to about an hour a day
- Within 6 months, he has lost 15 pounds, A1c dropped from 7.5% to 6.2%, and his BMI is down to 31 mg/m²
Summary
1. 18.5% of children in US are obese; 3.4 – 5.8 million with severe obesity; 7.1% annual increase in youth Type 2 DM
2. Causes of obesity and Type 2 DM multifactorial
3. Diagnosis:
   1. Obesity: BMI > 95%; Severe Obesity: BMI > 120% of the 95th percentile
   2. DM: A1c ≥ 6.5%, FBG ≥ 126, 2-h OGTT: glucose ≥ 200, random glucose ≥ 200 with symptoms
4. Management:
   1. Lifestyle modifications (dietary, exercise)
   2. Metformin +/- insulin
   3. Could consider other pharmacotherapeutic options (not yet approved)

EXTRA SLIDES

Diabetes Mellitus: What Causes Symptoms
• Increased blood glucose (hyperglycemia) resulting from defects in insulin secretion, insulin action, or both
  • Glucose levels above ~ 180 mg/dl exceed kidney’s ability to filter the glucose load, resulting in appearance of glucose into the collecting ducts of the kidney and into the urine (glucosuria)
  • Osmotic pressure from glucose draws additional water into the collecting tubules, resulting in increased urine output (polyuria)
  • Large volumes of urine output lead to decreased effective circulating plasma volume triggering receptors that stimulate thirst and water/fluid intake (polydipsia)
  • Chronic hyperglycemia leads to catabolic state – results in muscle and fat breakdown, weight loss