Type 2 Diabetes in Children and Adolescents

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Before we start…

- No financial disclosures

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Objectives

- Pathophysiology of type 2 diabetes in pediatrics
- Discuss updated standards of care from ADA-2020 for the management of type 2 diabetes in pediatrics
- Discuss diagnostic challenges
- Treatment options for type 2 diabetes in pediatrics
- Possible co-morbidities and how to screen and monitor

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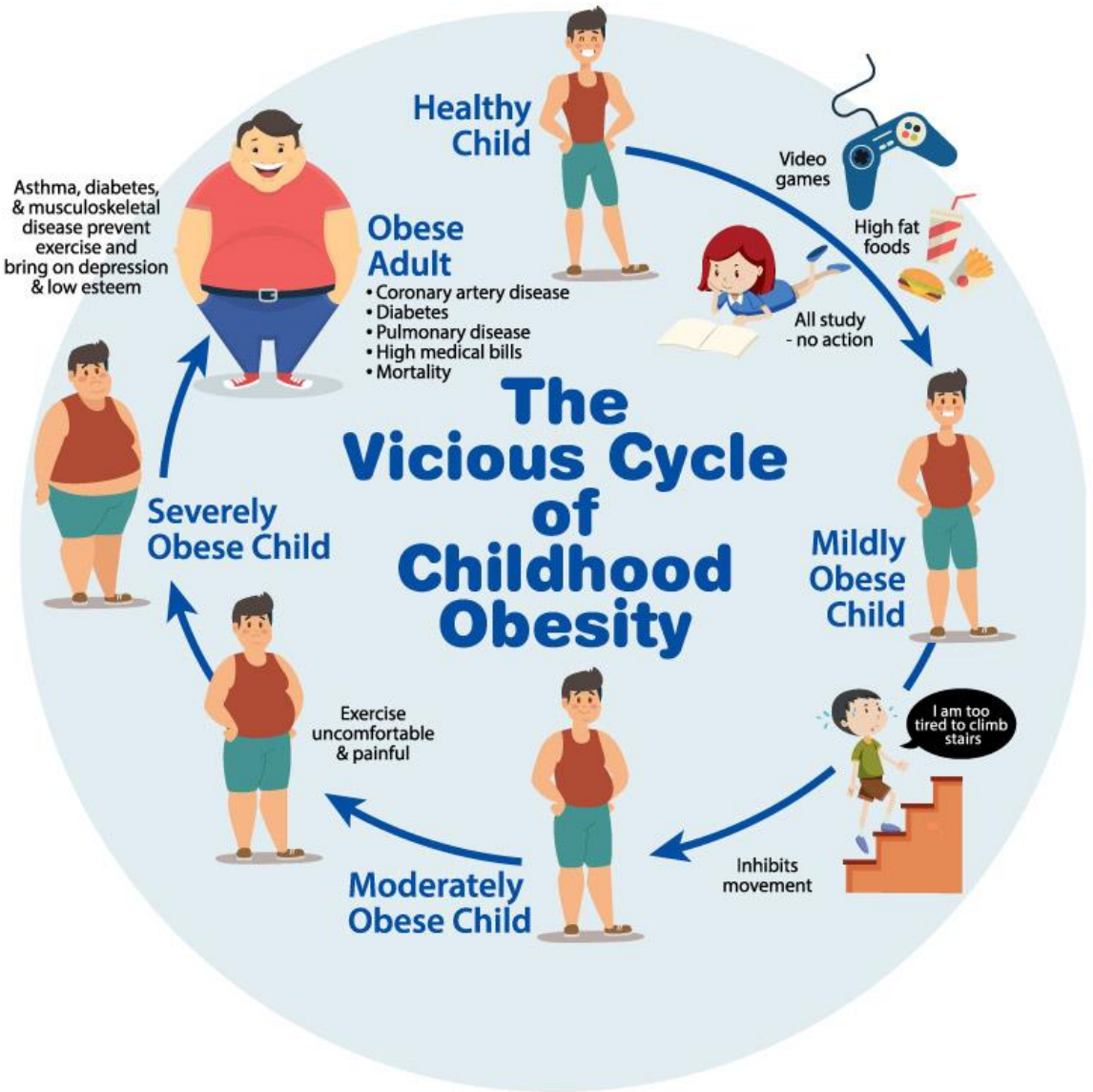
Obesity



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Definitions

- 2007 AAP obesity and overweight definitions
- Under 2 years: Overweight = weight-for-length >95th percentile for age/sex
- Over 2 years: Overweight = BMI 85-94th percentile for age/sex
- Obese = BMI >95th percentile for age/sex

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Introduction

- Type 2 diabetes in youth has increased over the past 20 years
  - May increase even more now after COVID-19
- Recent estimates suggest an incidence of 5,000 new cases per year in the US
- Growing evidence suggests that type 2 diabetes in youth is not only different from type 1 diabetes but also differs from type 2 diabetes in adults.
  - B cell function declines at an accelerated pace and have higher risk for complications
- Disproportionately impacts youth of ethnic and racial minorities and can occur in complex psychosocial and cultural environments, which may make it difficult to sustain healthy lifestyle changes.

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Pathophysiology

- Glucose homeostasis is maintained by a balance between insulin secretion from the b-cells and sensitivity to insulin in skeletal muscle, adipose tissue, and liver.
- When insulin sensitivity declines, insulin secretion must increase to maintain glucose tolerance, and, in most youth, decreased insulin sensitivity due to puberty and/or obesity is compensated by increased insulin secretion.
- Overweight and obesity are major acquired contributors to the development of insulin resistance, particularly in the face of the physiologic insulin resistance characteristic of puberty.
  - Adolescents with obesity who develop type 2 diabetes have severe peripheral and hepatic insulin resistance, with about 50% lower peripheral insulin sensitivity than peers with obesity without diabetes
  - Additional abnormalities in youth with type 2 diabetes include impaired glucose sensitivity of insulin secretion, lower serum adiponectin concentrations, and reduced incretin effect

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Pathophysiology

- Cross-sectional and longitudinal studies in youth with obesity along the spectrum of glycemia from normoglycemia to prediabetes to type 2 diabetes show that b-cell failure with declining insulin secretion relative to insulin sensitivity results in prediabetes and type 2 diabetes in high-risk youth
- Prior to reaching the ADA defined fasting and oral glucose tolerance test (OGTT)-stimulated glycemic cut points for the diagnosis of prediabetes they already demonstrate declining b-cell function relative to insulin sensitivity
- Also, youth with A1C in the at-risk/ prediabetes category (5.7 to ,6.5%) demonstrate impaired b-cell function compared with those with A1C <5.7%

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Pathophysiology

- A combination of obesity, genetics, the hormonal milieu, incretins and metabolic alterations, such as glucotoxicity and/or lipotoxicity, are likely to contribute to deteriorating b-cell function against the backdrop of insulin resistance.
- Based on the baseline data from the Restoring Insulin Secretion (RISE) study there appear to be important differences in insulin sensitivity and b-cell function between youth and adults with similar degrees of dysglycemia, including greater insulin resistance for any degree of adiposity and greater insulin secretion for any degree of insulin resistance in youth compared with adults.

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Screening and Diagnosis

- Type 2 diabetes typically occurs in adolescents at mid puberty (about 14 y/o in TODAY study)
  - Most likely precipitated by the physiologic, but transient, pubertal insulin resistance aggravating the preexisting metabolic challenges of obesity.
  - Cross-sectional and longitudinal studies show that insulin sensitivity declines by 25–30% as youth transition from prepuberty to puberty
  - In the presence of normally functioning b-cells, puberty-related insulin resistance is compensated by increased insulin secretion/hyperinsulinemia.
  - In youth who are predisposed to develop prediabetes and/or type 2 diabetes, b-cell compensation is inadequate.

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Screening and Diagnosis

- Risk based screening for prediabetes and/or type 2 diabetes should be considered:
  - after the onset of puberty or 10 years of age, whichever occurs earlier, with overweight or obesity and who have one or more additional risk factors for diabetes
    - Maternal history of diabetes or GDM during the child's gestation
    - Family history of type 2 diabetes in first- or second-degree relative
    - Race/ethnicity (Native American, African American, Latino, Asian American, Pacific Islander)
    - Signs of insulin resistance or conditions associated with insulin resistance (acanthosis nigricans, hypertension, dyslipidemia, polycystic ovary syndrome, or small-for-gestational

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Screening and Diagnosis

- If tests are normal, repeat testing at a minimum of 3-year intervals or more frequently if BMI is increasing
  - Fasting plasma glucose
  - 2-h plasma glucose during a 75-g oral glucose tolerance test,
  - HbA1C-limited data in diagnosis of type 2 in pediatrics
  - Children and adolescents with overweight or obesity in whom the diagnosis of type 2 diabetes is being considered should have a panel of pancreatic autoantibodies tested to exclude the possibility of autoimmune type 1 diabetes

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Table 2—Criteria for the diagnosis of prediabetes and diabetes

Prediabetes
A1C 5.7% to <6.5% (39 to <48 mmol/mol). The test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay.
IFG: fasting glucose ≥100 but <126 mg/dL (≥5.6 but <7.0 mmol/L).
IGT: 2-h plasma glucose ≥140 but <200 mg/dL (≥7.8 but <11.1 mmol/L) during an OGTT. The test should be performed as described by the World Health Organization, using a glucose load containing the equivalent of 1.75 mg/kg (max 75 g) anhydrous glucose dissolved in water.*
Diabetes
A1C ≥6.5% (≥48 mmol/mol). The test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay.*
OR
FPG ≥126 mg/dL (7.0 mmol/L). Fasting is defined as no caloric intake for at least 8 h.*
OR
2-h plasma glucose ≥200 mg/dL (11.1 mmol/L) during an OGTT. The test should be performed as described by the World Health Organization, using a glucose load containing the equivalent of 1.75 mg/kg (max 75 g) anhydrous glucose dissolved in water*
OR
In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose >200 mg/dL (11.1 mmol/L).

FPG, fasting plasma glucose; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; max, maximum. *In the absence of unequivocal hyperglycemia, result should be confirmed by repeat testing.

Diagnostic Challenges

- Given the current obesity epidemic, distinguishing between type 1 and type 2 diabetes in children can be difficult.
- Overweight and obesity are common in children with type 1 diabetes and diabetes-associated autoantibodies and ketosis may be present in pediatric patients with features of type 2 diabetes (including obesity and acanthosis nigricans.
  - The presence of islet autoantibodies has been associated with faster progression to insulin deficiency
  - At onset, DKA occurs in 6% of youth with type 2 diabetes

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Diagnostic Challenges

- In the TODAY study, of the 1,206 youth clinically diagnosed with type 2 diabetes and screened for circulating GAD65 and IA2 antibodies:
  - 118 (9.8%) were antibody positive.
  - Even though these Ab+ individuals had clinical characteristics that overlapped with the antibody negative youth, they were less likely to be obese, have features of metabolic syndrome, have a family history of diabetes, be female, or be from a minority race/ethnicity, indicating a phenotype more similar to their peers with type 1 diabetes

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Diagnostic Challenges

- Ab- youth with obesity are more insulin resistant than Ab+ youth with obesity, while Ab+ youth have more severe insulin deficiency.
- Fasting and stimulated C-peptide are significantly lower in Ab- youth with obesity and diabetes
- Moreover, Ab- youth are more likely to exhibit features of the metabolic syndrome (elevated systolic blood pressure and ALT), while Ab+ youth have significantly more frequent ketonuria at initial presentation.
- The reported rates of positive pancreatic autoantibodies in youth clinically diagnosed with type 2 diabetes vary from 10% to 75%, likely depending on the ratio of type 1 and type 2 diabetes in the population.

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Diagnostic Challenges

- The distinction between these forms of diabetes in youth with obesity has important implications for treatment since Ab+ youth present more like individuals with type 1 diabetes, progressing to insulin requirement more rapidly and are at risk for other autoimmune disorders.
  - Measurement of pancreatic autoantibodies is recommended in all youth with clinical characteristics of type 2 diabetes. This testing should include GAD65 and IA2 antibodies, along with insulin autoantibody in individuals who have not yet been exposed to exogenous insulin

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Management

- Treatment of type 2 diabetes should include lifestyle management, diabetes self-management education, and pharmacologic treatment.
- Initial treatment of youth with obesity and diabetes must take into account that diabetes type is often uncertain in the first few weeks of treatment
  - A substantial percentage of youth with type 2 diabetes will present with clinically significant ketoacidosis
- Initial therapy should address the hyperglycemia and associated metabolic derangements

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Glycemic Targets

- A1C should be measured every 3 months.
  - A reasonable A1C target for most children and adolescents with type 2 diabetes 7%.
- Glycemic targets should be individualized, taking into consideration long term health benefits of more stringent targets and risk for adverse effects, such as hypoglycemia.
  - A lower target A1C in youth with type 2 diabetes when compared with those recommended in type 1 diabetes is justified by lower risk of hypoglycemia and higher risk of complications
- In TODAY study, individuals with an A1C of >6.3% after 3 months of metformin or an increasing A1C, even in the non diabetes range, reflected a greater degree of b-cell dysfunction.
- Individuals with youth-onset type 2 diabetes have high rates of complications many of which are associated with poor glycemic control
  - Taken together, this evidence suggests that a more stringent A1C target can and should be attained in youth with type 2 diabetes

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Management

- Lifestyle management
  - Dietary changes
    - Nutrition should focus on healthy eating patterns that emphasize consumption of nutrient dense, high-quality foods and decreased consumption of calorie-dense, nutrient-poor foods, particularly sugar added beverages
  - 30–60 min of moderate-to-vigorous physical activity at least 5 days per week
  - Goal: 7-10% decrease in excess weight
    - sustained weight losses >7% of excess body weight were associated with improvements in A1C, HDL, and C-peptide.

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Pharmacologic Management

- Current pharmacologic treatment options for youth-onset type 2 diabetes are limited to three approved drugs
  - Insulin, Metformin, Liraglutide
- Presentation with ketoacidosis or marked ketosis requires a period of insulin therapy until fasting and postprandial glycemia have been restored to normal
- Metformin therapy may be used as an adjunct after resolution of ketosis
- Initial treatment should also be with insulin when the distinction between type 1 diabetes and type 2 diabetes is unclear and in patients who have random blood glucose concentrations >250 or A1C >8.5%

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Pharmacologic Management

- When insulin treatment is not required, initiation of metformin is recommended.
- TODAY study found that metformin alone provided glycemic control in half of the subjects for 6 months
- To date, the TODAY study is the only trial combining lifestyle and metformin therapy in youth with type 2 diabetes
  - The combination did not perform better than metformin alone in achieving durable glycemic control.
- In the clinical setting, only a minority of youth with type 2 diabetes are on lifestyle management alone because it is often inadequate for achieving and maintaining the desired level of glycemic control and BMI improvement.

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Metformin

- Metformin is the preferred drug for initial treatment of type 2 diabetes in adults and youth.
  - The recommended approach to metformin initiation is to start with a dose of 500–1,000 mg/day and gradually escalate it every 1–2 weeks, depending on patient tolerability, to the recommended therapeutic dose of 1,000 mg b.i.d.
  - Slower dosage increase may be needed if gastrointestinal side effects occur
- In the TODAY study, 48.3% of youth with type 2 diabetes who were enrolled, with less than 2 years of diabetes duration, maintained adequate glycemic control on metformin alone for up to 6 years
  - However, youth were more likely than adults to require additional pharmacologic treatment to meet glycemic targets, with the other 51.7% of youth on metformin requiring insulin by 4 years

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Initial therapy

- Asymptomatic youth with presumptive type 2 diabetes who present in a stable metabolic state and have A1C <8.5% should be started on metformin as initial therapy, if renal functionis normal.
- Asymptomatic patients with A1C >8.5% may also be given an initial trial of metformin if family is motivated

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Insulin and Metformin

- Youth with marked hyperglycemia (blood glucose >250 mg/dL and/or A1C >8.5%) without acidosis at diagnosis but who are symptomatic with polyuria, polydipsia, nocturia, and/or weight loss should be treated initially with basal insulin and titrating metformin.
- In patients with ketoacidosis at diagnosis, treatment with subcutaneous or intravenous insulin should be initiated to rapidly correct the hyperglycemia and the metabolic derangement.
- Once acidosis is resolved, metformin should be initiated while subcutaneous insulin therapy is continued
- Once glycemic stability is achieved, insulin may not be needed. Limited

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Insulin and Metformin

- In patients initially treated with insulin and metformin who are meeting glucose targets based on home blood glucose monitoring, insulin can be tapered over 2– 6 weeks by decreasing the insulin dose 10–30% every few days
- When the individualized glycemic target can no longer be met with metformin alone, or if metformin intolerance or renal insufficiency develops, insulin therapy should be initiated.
- Because studies indicate that adherence with insulin therapy is a challenge in youth with type 2 diabetes starting with a single daily dose of a long-acting insulin may be preferred.
- If the combination of metformin at the maximum tolerated dose plus basal insulin at a maximum dose of 1.5 units/kg/day is ineffective at achieving the glycemic target, medication adherence should be actively addressed.

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Pharmacologic Management

- A randomized clinical trial in children aged 10–17 years with type 2 diabetes demonstrated the addition of subcutaneous liraglutide (up to 1.8 mg daily) to metformin (with or without basal insulin) as safe and effective to decrease A1C (estimated decrease of 1.06 percentage points at 26 weeks and 1.30 at 52 weeks)
- In June 2019, the U.S. Food and Drug Administration approved liraglutide injection for treatment of pediatric patients aged 10 y/o

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Victoza (liraglutide)

- FDA approved for pediatric use as of 6/10/19
- Approved for children 10 years and older with type 2 diabetes
- Injectable
- GLP-1 agonist
  - slows digestion, prevents the liver from making too much glucose, and helps the pancreas produce more insulin when needed.
- Adverse effects:
  - Hypoglycemia
  - Boxed Warning increased risk of thyroid C-cell tumors.
    - Can’t be used in those with MTC or MEN2

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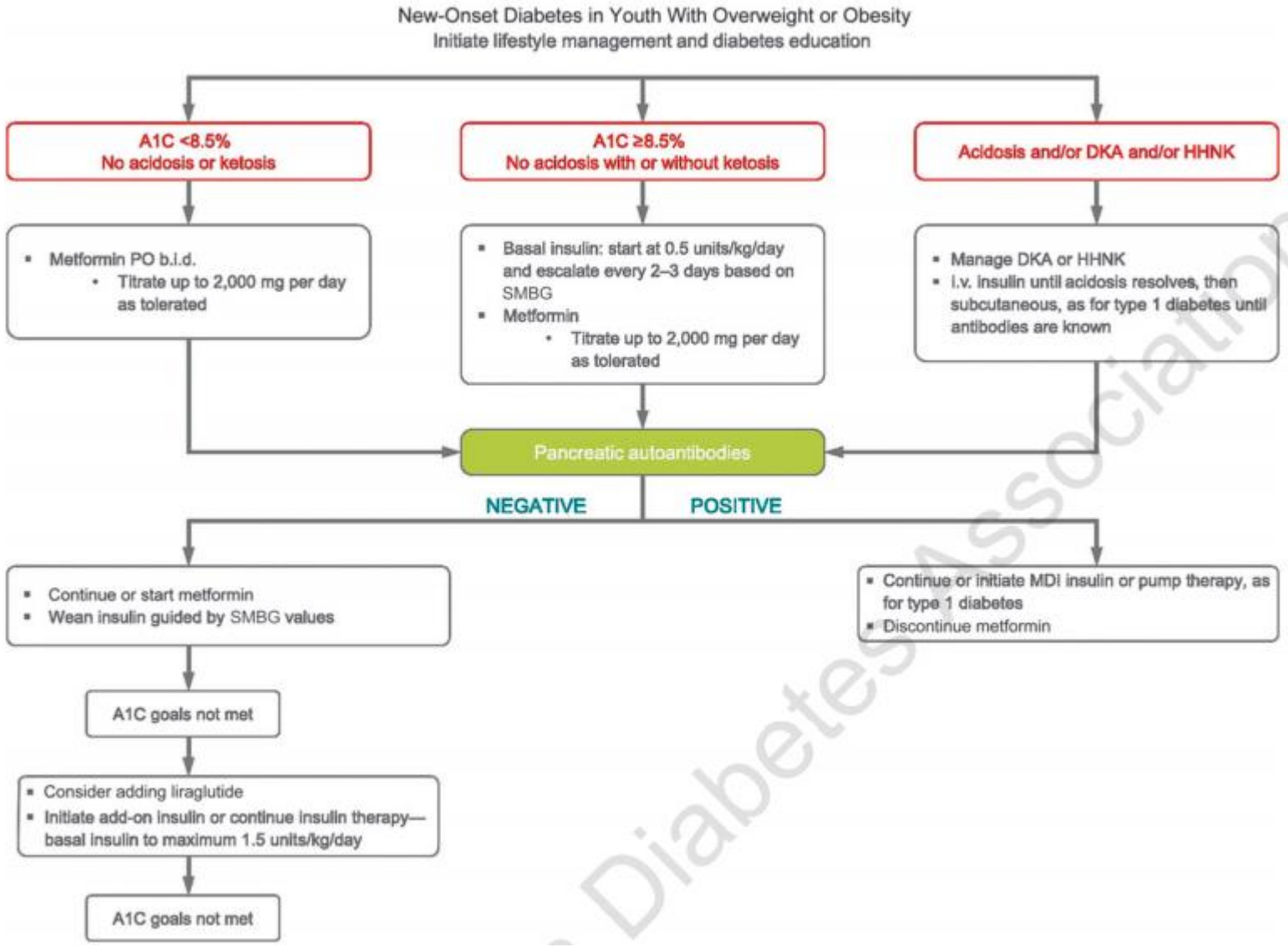
Management of type 2 Diabetes



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Metabolic Surgery

- The results of weight-loss and lifestyle interventions for obesity in children and adolescents have been disappointing, and no pharmacologic intervention is approved by FDA
- The guidelines used as an indication for metabolic surgery in adolescents generally include BMI >35 kg/m2 with comorbidities or >BMI 40 kg/m2 with or without comorbidities
- Over the last decade, weight-loss surgery has been increasingly performed in adolescents with obesity.
  - Small retrospective analyses and a recent prospective multicenter nonrandomized study suggest that bariatric or metabolic surgery may have benefits in obese adolescents with type 2 diabetes similar to those observed in adults.
  - Teenagers experience similar degrees of weight loss, diabetes remission, and improvement of cardiometabolic risk factors for at least 3 years after surgery
  - No randomized trials have yet compared the effectiveness and safety of surgery to those of conventional treatment options in adolescents

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Prevention and management of complications

Nephropathy

- Blood pressure should be measured at every visit.
  - If blood pressure is 90th percentile for age, sex, and height or, in adolescents 13 years, blood pressure is 120/80 mmHg increased emphasis should be placed on lifestyle management to promote weight loss.
  - If blood pressure remains above the 90th percentile or, in adolescents 13 years, blood pressure is 120/80 after 6 months, antihypertensive therapy should be initiated
    - Initial therapeutic options include ACE inhibitors or angiotensin receptor blockers.
  - Protein intake should be at the recommended daily allowance of 0.8 g/kg/day
  - Urine albumin-to-creatinine ratio should be obtained at the time of diagnosis and annually thereafter.
    - An elevated urine albumin-to-creatinine ratio (>30 mg/g creatinine) should be confirmed on two of three samples

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Dyslipidemia

- Lipid testing should be performed when initial glycemic control has been achieved and annually thereafter.
- Optimal goals are LDL cholesterol<100mg/dL HDL cholesterol >35 mg/dl and triglycerides <150 mg/dL.
- If lipids are abnormal, initial therapy should consist of:
  - optimizing glucose control
  - limit the amount of calories from fat to 25–30%, saturated fat to <7%, cholesterol <200 mg/day, avoid trans fats, and aim for <10% calories from monounsaturated fats for elevated LDL.
  - For elevated triglycerides decrease sugar and increase dietary omega-3 fatty acids
  - If LDL cholesterol remains >130 mg/dL after 6 months of dietary intervention
    - initiate therapy with statin, with a goal of LDL <100 mg/dL
    - If triglycerides are >400 mg/dl, optimize glycemia and begin fibrate, with a goal of <400 mg/dL fasting

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Other

- Neuropathy
- NAFLD
- Retinopathy
  - At diagnosis and annually thereafter
- PCOS

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Conclusions

- Type 2 diabetes has been increasing in the last few years
- Obesity in addition to pubertal insulin resistance may drive at risk individuals to develop type 2 diabetes
- Treatment should be multidisciplinary for a more successful outcome and to prevent complications

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