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Type 2 Diabetes in Kids

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Objectives

- Discuss Impact of Type 2 diabetes in pediatric populations
- Identify best practices in the care of pediatric populations with Type 2 diabetes.
- Discuss medications used in the Type 2 pediatric population
- Identify needs for standards and quality measures for pediatric populations with Type 2 diabetes.

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T2DM in KIDS: the Evolving Epidemic

- Epidemiology
- Incidence rate rose from 9.0 cases per 100,000 in 2002-2003 to 12.5 cases per 100,000 in 2011-2012 (32.6 per 100,000 for non-Hispanic Black youth, 18.2 per 100,000 for Hispanic youth, 12.2 per 100,000 for Asian/Pacific Islander youth, and 46.5 per 100,000 for Native American youth)
- Recent estimates suggest an incidence ~5,000 new cases per year in the United States. (Clinical Diabetes January 2022)
- Prevalence of T2DM in youth increased by 30.5 percent between 2001 and 2009
- Japan: 80% of new cases of DM are T2DM (4X rise in incidence)
- US: 8-45% of newly diagnosed patients with diabetes have T2DM
- Association with lower SES in developed countries

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OF INTEREST

In a report on the findings, published Aug. 17 in The Journal of Pediatrics, the investigators note it is unclear whether the virus infection itself was a factor in the rise, and they point to the switch to virtual learning and shutdown of sports and school activities as "environmental factors" that likely increased risk.

The researchers identified 3,113 pediatric patients during that period, age eight to 21, from 24 centers across the U.S. The average number of new diagnoses per year in the two pre-pandemic years increased from 825 to 1,463 during the first year of the pandemic, an increase of 77%.

Journal of Pediatrics 8/2022

USPSTF issues final recommendation on T2D screening in youth

There is insufficient evidence to assess the benefits and harms of screening children under age 18 for prediabetes and Type 2 diabetes, according to a US Preventive Services Task Force final recommendation published in the Journal of the American Medical Association. The incidence of Type 2 diabetes has increased in US youth from 9 cases per 100,000 children in 2002-2003 to 13.8 per 100,000 in 2014-2015. The task force recognized gaps in the literature, however, and encouraged further research on youth at risk for prediabetes and diabetes.

Diabetes PRO Smart Brief 9/2022

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Risk Factors for Developing Type 2 Diabetes in Kids

- Obesity: stronger in youth than in adults (80% obese, 10% overweight, <10% <85%ile)
- Yet not all are obese!
- Positive family history:
- 50-75% of children with T2DM have at least one affected parent. The offspring of a parent with T2DM has an estimated 20 percent risk of developing T2DM by late adulthood, 30 percent if both parents are affected
- In monozygotic twins with one affected twin, the other twin has a >90 percent chance of developing diabetes
- Ethnic differences: increased in Native American youth (8X NHW) and Non-Hispanic Black youth (5X NHW) and Hispanics (4X NHW).
- Girls>Boys
- Low birthweight
- Gestational diabetes. In the SEARCH for Diabetes in Youth study, gestational or pre-gestational diabetes and intrauterine exposure to maternal obesity were independently associated with T2DM in adolescents, and both risk factors were present in 47 percent of the SEARCH cohort

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Presentation of T2DM in Kids

- Asymptomatic – 40 percent
- Symptomatic (eg, polydipsia and polyuria) without ketonuria or acidosis – 57 to 70 percent
- Diabetic ketoacidosis (DKA) – 5 to 12 percent
- Hyperosmolar hyperglycemic state (HHS) – Uncommon

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Obesity and Insulin Resistance The path

1. Insulin resistance, normal glucose tolerance
2. Insulin resistance, increased PP glucose, abnormal GTT
3. Insulin resistance, Increased Fasting and PP Glucose (Pre-diabetes)
4. Diabetes, Insulin Resistance OGTT Positive
5. Diabetes (80% of beta cell function lost at diagnosis)

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"Prediabetes" in Kids

- Definitions
- Hemoglobin A1c (A1C) values between 5.7 and 6.4 percent (39 to 47 mmol/mol)
- Impaired fasting glucose – Fasting plasma glucose (FPG) ≥100 to 125 mg/dL (≥5.6 to 6.9 mmol/L)
- Impaired glucose tolerance – Plasma glucose ≥140 to 199 mg/dL (≥7.8 to 11.0 mmol/L) measured two hours after a glucose load of 1.75 g/kg (maximum dose 75 g) in an oral glucose tolerance test (OGTT)
- National Survey: Prevalence of prediabetes in youth 12 to 18 years of age was 18 percent

  26 percent among those with obesity
- Males (22.5 percent) versus females (13.4 percent)
- Annual rescreening for T2DM is generally recommended assuming an OGTT is not diagnostic for diabetes (higher sensitivity).
- Studies of T2DM progression in IGT patients, 8 percent progressed to T2DM with median duration of follow-up of 2.9 years and 65 percent reverted to normal glucose tolerance, markedly higher for non-Hispanic Black adolescents compared with White adolescents.
- Recommendation: patients with prediabetes should be engaged in intensive lifestyle interventions similar to the nonpharmacologic therapy recommended for patients with established T2DM.

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Treatment of Prediabetes, does it help?

- RISE (Restoring Insulin Secretion) consortium assessed the tempo of beta cell function decline in individuals with prediabetes or early diabetes by performing serial assessments of insulin secretion and insulin sensitivity using hyperglycemic clamps and OGTTs
- RISE pediatric medication study, treatment with metformin for 12 months, or insulin glargine for three months followed by metformin for nine months, failed to prevent deterioration of beta cell function at 12 months and upon retesting at 15 months
- In the adolescent subgroup with prediabetes (IGT), 6 percent progressed to T2DM at 15 months despite the medications. *In adults, similar treatments improved insulin secretion and preserved glycemic control*
- *Adolescents were more insulin resistant, with a more rapid decline in beta cell function over time compared with adults*
- **In conclusion: the path to diabetes appears different (and more aggressive) in children. We must aggressively intervene when faced with prediabetes in youth**
- **lifestyle management**
- **addition of medications?**

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Screening in asymptomatic kids: who, when and how often?

- **Who:**
- **Obese or overweight:** BMI ≥85th percentile AND two or more:
- T2DM mellitus in a first- or second-degree relative
- Member of a high-risk racial/ethnic group: Native American, African American, Latino, Asian American, or Pacific Islander
- Maternal history of diabetes or gestational diabetes during the child's gestation
- Signs of insulin resistance or conditions associated with insulin resistance (eg, hypertension, dyslipidemia, acanthosis nigricans, polycystic ovary syndrome [PCOS], or small for gestational age birth weight)
- **When:** after the onset of puberty or ≥10 years, whichever occurs earlier
- **How often**: a minimum of every three years or more frequently if BMI is increasing. More frequently (eg, annually) in patients with marked obesity or strong evidence of insulin resistance, or in patients with borderline results.

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Which Test in Asymptomatic Children?

- Hemoglobin A1c —if certified by NGSP and performed in a certified laboratory *and not by using a point-of-care device*.
- A1C ≥6.5 percent X 2 = diabetes
- A1C of 5.7-6.4 = prediabetes
- A normal A1C does not exclude T2DM.
- Fasting plasma glucose (FPG) — used often but less sensitive than the OGTT
- FPG ≥126 mg/dL X 2 is sufficient to diagnose diabetes
- FPG ≥ 100-125 mg/dL is impaired fasting glucose (IFG) or prediabetes
- FPG values of 86-99 mg/dL have 2.1 X risk of T2DM and 3.4 X risk of prediabetes during adulthood
- Oral glucose tolerance test (OGTT) — More sensitive test. Use if clinical suspicion for diabetes is high despite an FPG or A1C that is nondiagnostic.
- The standard glucose load used for the OGTT in children is 1.75 g/kg, up to a maximum dose of 75 g. The 2-hour glucose after the glucose load is used for diagnosis.
- Plasma glucose ≥200 mg/dL is diagnostic of diabetes. Confirm on another day.
- Plasma glucose ≥140 to 199 mg/dL = impaired glucose tolerance (IGT)/prediabetes

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Diagnosis of Type 2 Diabetes in Kids (any of the following = diagnosis of T2DM)

1.BG>200 mg/dl, with symptoms (polyuria, polydipsia, weight loss)

2.2 fasting (8 hr) blood sugar values >125 mg/dl

3.Hemoglobin A1c (A1C) ≥6.5 percent (48 mmol/mol). The test should be performed in a laboratory (not a point-of-care device) using a method that is certified by the National Glycohemoglobin Standardization Program (NGSP).

4.BG > 200 mg/dl at 2-hour point of oral glucose tolerance test (1.75 g/kg po, max 75 grams). This needs to be repeated for confirmation.

- Note:

1.Approximately 30% of undiagnosed patients have a normal fasting glucose (adult data). This is quite common in girls with Polycystic Ovarian Syndrome (PCOS).

2.Although patients usually have elevated insulin levels at diagnosis, adolescents with T2DM can have ketoacidosis at diagnosis (and relatively low insulin levels) due to chronic hyperglycemia and "glucotoxicity

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Diagnosis of T2DM in Kids, challenges

- Historically, testing of pancreatic autoantibodies: if positive, consider Type 1 (10%)
- Anti-glutamic acid decarboxylase (GAD65) and tyrosine phosphatase insulinoma-associated antigen 2 (IA2) antibodies
- Insulin autoantibodies (IAA)
- Beta cell-specific autoantibody to zinc transporter 8 (ZnT8)
- *Why?*
- Important to distinguish between the two diseases if possible
- Unfortunately, there is overlap between the two disorders regarding both insulin resistance and pancreatic autoantibodies
- *No set of criteria or diagnostic test can consistently distinguish between T1DM and T2DM.* Therefore, differentiating between the two types is based upon a combination of the clinical presentation and history, often supported by laboratory studies

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POSITIVE FINDINGS FOR TYPE 2 STANDARDS IN CARE

- During clinic visit, do labs for Lipid panel, Chemistry, Thyroid and get Urine Microalbumin.
- Be aware that as in adult Type 2, there may already be HTN and Hyperlipidemia present.
- Treat Hypertension, follow Lipids as glucose numbers come down.

  treat lipids if not down with decrease in glucose
- Teach child and family blood glucose monitoring.
- Evaluate family for ability to change lifestyle, including food and care costs.
- In some cultures, they may agree, knowing that to eat healthier is a financial hardship. (frequently will tell you what you want to hear, yet not follow through.
- If possible, refer to Endocrinology

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Treatment of T2 DM in Kids: General Principles

1. Glycemic Targets similar to adults (HgbA1c < 7%, pre-prandial glucose 80-120 mg/dl, post-prandial glucose < 180 mg/dl)
2. Target improvements in insulin resistance and insulin secretion
3. Management of obesity and its comorbidities using lifestyle modification
4. Evaluation, screening, and management of hyperlipidemia and hypertension
5. Evaluation, screening, and management of complications of T2DM
6. Application of culturally sensitive approaches to management strategies

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Treatment of T2DM in Kids

- Weight goals (weight loss improves insulin sensitivity and improves beta cell function):
- 7 to 10% in those who have completed linear growth
- BMI <85th percentile for age and sex in those still growing
- Weight reduction versus weight maintenance depends on the age of the patient, the degree of obesity, and the presence of comorbidities
- For most youth with T2DM, weight reduction rather than weight maintenance is indicated (0.5-1.0 lb/week in younger, 1-2 lb/week in adolescents)
- **Dietary prescription** — gradual change of family and individual dietary habits (culturally sensitive, adapted to the individual)
- Decrease portions
- Substitute a fruit or vegetable for a carbohydrate-rich food
- Eliminate high-caloric beverages (sugar-containing soft drinks, juices) and replace them with water or calorie-free beverages
- Decrease frequency of eating out and increase family meals at home. Provide advice for "eating out"

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Exercise Recommendations for Kids with T2DM

- Increased physical activity, independent of its effect on body weight, improves insulin sensitivity
- Moderate to vigorous physical activity for at least one hour daily
- Strength training at least three times weekly
- Decrease sedentary behaviors, eg, limiting nonacademic "screen time" (eg, television, video game, and computer) to less than two hours daily

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Metformin

- Action: decreases hepatic glucose output, increased hepatic and muscular insulin sensitivity
- FDA Approved for children: yes
- Typical dosing: 500 mg/d→1000 mg BID (Max 850 mg TID). Liquid available.
- Hypoglycemia Risk? No
- Weight gain? No (often loss)
- Precautions: illness, hypoxia, CHF, dehydration (including contrast agents): theoretical risk of life-threatening metabolic acidosis
  - Weight decreased 4.35 kg on metformin vs placebo
  - BMI decreased 1.26 kg/m2 over 6 months
  - Fasting insulin decreased

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INSULIN for T2DM for Metformin monotherapy failure

- Basal insulin:
- Insulin Glargine (U-100 or U-300), detemir, or degludec (U-100 or U-200) at bedtime with a starting dose of 0.2 units/kg per day
- Adjusted as needed to achieve targets for blood glucose and A1C (FPG <100 mg/dL; A1C <7 percent)
- Mealtime insulin: added if decompensation of glycemic control (glucose ≥250 mg/dL or A1C >8.5 percent or ketoacidosis). Hold metformin if acute metabolic decompensation, such as ketoacidosis, or when A1C exceeds 12 percent.

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Insulin Secretagogues: Incretin Mimetics (GLP1 analogs)

- Action: mimics the action of GLP-1 (glucagon like peptide-1):
- stimulation of insulin secretion only when blood sugar is high (restoring the first phase insulin response)
- suppression of glucagon release (improved post-prandial BGs)
- slows gastric emptying and reduces food intake (most patients in the long-term clinical studies experienced weight loss)
- increased beta cell mass in animal studies

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Liraglutide (GLP-1 analog)

- Approved by the FDA in 2019 for use in pediatric patients with T2DM over the age of 10
- By subcutaneous injection once daily
- Promotes weight loss, probably due to delayed gastric emptying and possibly through central effects on appetite
- Dosing: 0.6, 1.2 or 1.8 mg daily
- Higher dose (3.2 mg daily) is approved for Obesity in adolescents (Saxenda)
- Other GLP-1 analogs are being studied in children

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ELLIPSE TRIAL (liraglutide adjunct to metformin)

- Pediatric patients (10 to <17 years old), 26-week trial
- Randomized trial of 134 subjects with T2DM led to FDA approval in 2019
- Results: Liraglutide + metformin-> A1c lower by 0.64%, improved lipids, 86% no insulin rescue
- Metformin alone A1c higher by 0.42%, 67% no insulin rescue
- Open-label extension for 1 year: modest weight loss (-1.9 kg) compared with metformin alone (+0.87 kg)
- Adverse effects: GI (N/V), 25-30% vs 9-13% in metformin alone group

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BYDUREON, exenatide, Bydureon, Bcise (pen)

- BYDUREON Bcise once weekly(extended release) exenatide is indicated as an adjunct to diet and exercise to improve glycemic control in adults and pediatric patients aged 10 years and older with type 2 diabetes mellitus
- Should not use Bydureon if you have a personal or family history of thyroid cancer, if you have multiple endocrine neoplasia type 2 (MEN 2, a cancer that can affect the thyroid, parathyroid, and adrenal glands)
- 10 years and older:
  Extended-release: 2 mg subcutaneously once every 7 days (weekly)
  -May administer any time of day, with or without meals; see dose adjustments for information on missed doses and changing administration day

  Comments:
  -Extended-release exenatide is not recommended as first-line therapy because of the uncertainty of the risk of thyroid C-cell tumors.
  -This drug is not indicated for use in patients with type 1 diabetes.

  Use: As an adjunct to diet and exercise to improve glycemic control in pediatric patients 10 years and older with type 2 diabetes mellitus.

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Bariatric Surgery

- Recent data suggest that bariatric surgery may be effective in the treatment of type 2 diabetes and has emerged as a potential treatment for obesity because it causes substantial and durable weight reduction.
- (TODAY) study examined time to treatment failure in children and adolescents with new-onset type 2 diabetes. The trial defined treatment failure as an HbA_{1c} of >8% for 6 months or metabolic decompensation requiring insulin therapy, average time to failure of 11 months.
- Surgical outcome studies that have included 10 or more adolescent participants with type 2 diabetes and at least 1 year of follow-up data, the results have generally demonstrated excellent weight loss and diabetes remission or improvement
- Surgical complications such as anastomotic leakage was infrequently observed after each type of procedure. Upper endoscopic procedures (including stricture dilations)
- Nutritional deficiencies, commonly seen as vitamin B_{12}, thiamine, and vitamin D deficiency, are also a potential significant short- and long-term complication of adolescent bariatric surgery
- One-third of adult's experience relapse to diabetes within 5 years of initial remission.
- Relapse rates in children and adolescents are yet to be published or evaluated.
- ***Recent study sets age for surgery 13 y/o in conjunction with gastroenterology care.

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Other agents not currently used

- Thiazolidinediones, such as rosiglitazone and pioglitazone: not approved by the FDA for use in pediatric patients
- Sulfonylureas: not used (weight gain)
- Dipeptidyl peptidase-4 (DPP-4) inhibitors (sitagliptin) increase insulin production and decrease the liver's production of glucose (weight neutral, no hypoglycemia). Linagliptin is currently being studied. (Currently in Stage 3 study)
- Amylin analogs (pramlintide, SQ): slow gastric emptying and suppress glucagon secretion, approved for use in adult patients taking concomitant insulin. Not approved in Pediatrics.
- Alpha-glucosidase inhibitors (acarbose) delay the absorption of carbohydrates; lipase inhibitors (Orlistat) reduce the absorption of fat. Less effective, with GI side effects (diarrhea, soiling)
- Sodium-dependent glucose cotransporters (SGLT2) inhibitors (canagliflozin, dapagliflozin, empagliflozin, sotagliflozin [a dual SGLT1/2 inhibitor]) increase urinary glucose excretion, reduce blood glucose levels, and improve A1C. In addition, there is an associated decrease in body weight. (Currently in Stage 3 study)

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T2DM in Kids: a proposed treatment algorithm for diabetes control

- Asymptomatic Child: Lifestyle + metformin
- Consider liraglutide initially (and even in the Pre-diabetes phase) to help with weight loss
- Consider exenatide, to help with glucose control and weight loss
- Insulin for those who fail above therapy or significant ketosis is present.
- If insulin is used at diagnosis, consider adding metformin concurrently and weaning insulin as glucotoxicity wanes and blood sugars improve.

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IMPACTS

•Obesity and Type 2 diabetes in pediatrics is increasing at an alarming rate.

•This is will impact the healthcare environment by increasing the number of young adults with chronic diseases not generally seen until later in life.

- Depression will increase in this population

Insurance coverage for medication other than Metformin is difficult to get approved, Liraglutide approved but requires multiple prior authorization attempts.

•Using a sensor such as Libre, also refused in most cases.

•Perception by family, that Type 2 is not as serious as other concerns

•Discomfort by providers in treating any type of pediatric diabetes is just "too complex"

•Adolescent attitudes on self-care.

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CONCLUSIONS

- Type 2 in pediatrics is becoming a serious problem, the impact on the child, family and healthcare system are going to become more apparent as time goes on.
- As Diabetes care and education specialists and providers, we need to ensure appropriate care is given to this group.
  - Encouraging healthy lifestyle for our patients and families.
  - Using prediabetes and PCOS as a warning to increase education.
    - Discussing options to screen time.
    - Discussing options to diet as usual.
    - Discussing ideas to engage this age group.

  Continue to develop treatments for this group.

  Continue to encourage insurers to provide adequate quality measures.

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Thank You
Questions???

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