Type 2 Diabetes in Children and Adolescents

Ann Marie Straight MD
LTC, USA, MC
Pediatric Endocrinologist
BAMC

Overview

1) Epidemiology
2) Pathogenesis of T2DM
3) Symptoms at presentation
4) Screening for asymptomatic*
5) Making the Diagnosis T2DM*
6) Lab evaluation
7) Treatment
8) Management of co-morbid conditions
9) Follow-up
10) Hyperglycemic Hyperosmolar Syndrome

*Based on recommendations made in the 2011 ADA Clinical Practice Guidelines.
Epidemiology Type 2 DM

- T2DM considered an adult disease until recently
- ↑ Prevalence of T2DM has followed ↑ prevalence of obesity.
- SEARCH for Diabetes in Youth
  - T2DM uncommon < 10 yo regardless of race/ethnicity
  - Incidence ↑ 10-14 yo and is highest in 15-19 yo
  - T2DM 20% new cases DM 10-19 yo
- Can account for as much as 50% of new cases in AA, AI, API, H youth

Pathophysiology of T2DM

Normal glycemic control requires:
1) Sensing of the glucose concentration by β cells
2) Synthesis and release of insulin
3) Binding of insulin to receptors
4) Increased glucose uptake by muscles, fat, and liver
5) Decreased glucose production by the liver

Type 2 DM results from a progressive insulin secretory defect on the background of insulin resistance.

Pathophysiology of T2DM

- 1) Insulin resistance
- 2) β-cell dysfunction
  - Inherited
  - Acquired from glucotoxicity and lipotoxicity
- 3) Relative or absolute insulin deficiency

Progression to Type 2 Diabetes

- Preexisting factors
  - Obese, sedentary, dietary habits
- Insulin resistance
- Impaired Glucose Tolerance
- β-cell exhaustion
- Inadequate insulin for the degree of insulin resistance
- Type 2 DM

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Insulin Resistance

Hyperinsulinemia + Normal glucose tolerance
Hyperinsulinemia + Postprandial hyperglycemia

Type2DM
1) Insulin resistance
2) Hepatic glucose production

Risk factors and markers:
1) Minority population
2) Family history of T2DM
3) IUGR - 2-7 fold increased risk T2DM
4) Obesity
5) Puberty-increased growth hormone

Glucotoxicity
Lipotoxicity
Latent Autoimmunity

Symptoms of T2DM
• Insidious onset
• Symptoms x months to years without realization
• Symptoms may include:
  – Wt loss
  – Fatigue
  – Blurred vision
  – Polyuria, nocturia, polydipsia, polyphagia
  – Recurrent candidal infections
• Many report no symptoms at time of diagnosis despite having high bgs
• CRITICAL TO SCREEN FOR DM

Screening for T2DM

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Testing Asymptomatic Children

Age ≥ 10 or signs of puberty

AND

BMI > 85%

AND

Any 2 of the following are present:
1) High-risk ethnic group (Native American, AA, Latino, Asian American, Pacific Islander)
2) Family hx of DM in first or second degree relatives
3) Signs of insulin resistance/conditions associated with insulin resistance (acanthosis nigricans, dyslipidemia, hypertension, PCOS, SGA)
4) Maternal hx of diabetes or gestational DM

Case Presentation: JS

HPI: 16 yo AA male w/ ADD presents for Concerta refill
PMHx: ADD, obesity, hyperlipidemia
Family Hx: Strong family hx T2DM, obesity, HTN. Mom had gestational DM and has had T2DM x 7 years on lantus and metformin.
Meds: Concerta
ROS: Denies wt loss, polyuria, polydipsia, nocturia, blurred vision

• PE: BP 123/66, HR 66
• Wt 110kg (>>97%)
• HT 173cm (25-50%)
• BMI 36.6 (>>97%)
• Well appearing
• Well hydrated
• +Acanthosis nigricans
• No HSM

Asymptomatic but screened because:
1) Age > 10
2) BMI > 85% AND
3) AA, family hx, hyperlipidemia, acanthosis

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Screening for DM

- Recommended studies include one of the following:
  - Fasting plasma glucose (FPG)
  - HgA1c
  - 2 hour OGTT

Screening for DM: HgA1c

<table>
<thead>
<tr>
<th>HgA1c (%)</th>
<th>Mean Plasma Glucose</th>
</tr>
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<tbody>
<tr>
<td>6</td>
<td>120</td>
</tr>
<tr>
<td>7</td>
<td>150</td>
</tr>
<tr>
<td>8</td>
<td>180</td>
</tr>
<tr>
<td>9</td>
<td>210</td>
</tr>
<tr>
<td>10</td>
<td>240</td>
</tr>
<tr>
<td>11</td>
<td>270</td>
</tr>
<tr>
<td>12</td>
<td>300</td>
</tr>
</tbody>
</table>

- RBC has a lifespan of 3-4 months
- RBCs bind irreversibly to glucose
- The percent of total hemoglobin that has glucose attached to it.
- Estimated blood sugar control for past 3-4 months.
- Normal is 5.6%.
- Convenient, does not require fasting
- Not influenced by acute stress or illness
- More expensive
- NHANES data indicate that HgA1c ≥ 6.5% may identify up to 1/3 fewer cases of DM than fasting bg ≥ 126

Screening for DM: OGTT

- No carbohydrate restriction prior to the study
- Fasting 8-10 hours
- Obtain baseline glucose
- If weight <43 kg, give 1.75g/kg
- Drink mixture-5 minutes
- Obtain 2 hour value
- Normal fasting <100
- Normal 2hr <140 mg/dL

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Diagnosing DM

- Fasting plasma glucose (FPG) ≥ 126mg/dl
- 2hr plasma glucose of ≥ 200 mg/dl during an oral glucose tolerance test
- Hemaglobin A1c ≥ 6.5%
- In the absence of unequivocal hyperglycemia, results should be confirmed by repeat testing
- Symptoms of hyperglycemia and random plasma glucose ≥ 200mg/dl

Diagnosing Prediabetes

- Impaired fasting glucose (IFG)
  - FPG 100-125 mg/dl
- Impaired glucose tolerance (IGT)
  - 2hr PG 140-199 mg/dl
- HgA1c 5.7-6.4 %
- Increased risk for developing DM and cardiovascular disease (CVD)
- Associated with obesity, dyslipidemia (high TG, low HDL), and HTN
Additional Studies at Diagnosis

**Chem panel**
- Degree of hyperglycemia
- Acidosis
- Hypernatremia, hypokalemia
- +/- Serum osmolality

**Insulin and c-peptide**
- Usually elevated in T2DM
- May be LOW due to glucose-toxicity and impaired B cell function
- Re-test 3-6 months
- IGFBP1 is suppressed by insulin. ↑T1 and ↓T2

**Antibody levels**
- Islet cell, insulin Ab, GAD Ab
- 20% of children with T2DM will have +GAD Ab
- Positivity increases the likelihood that insulin therapy will be needed

**HgA1c**
- Duration of highs
- Choice of initial therapy

<table>
<thead>
<tr>
<th></th>
<th>Type 1 DM</th>
<th>Type 2 DM</th>
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</thead>
<tbody>
<tr>
<td>Family Hx</td>
<td>3-5%</td>
<td>74-100%</td>
</tr>
<tr>
<td>Age</td>
<td>Variable</td>
<td>&gt;10, pubertal</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>Rare</td>
<td>Common</td>
</tr>
<tr>
<td>Symptoms</td>
<td>Days/Weeks</td>
<td>Months</td>
</tr>
<tr>
<td>BMI at Dx</td>
<td>&lt;75%</td>
<td>&gt;85%</td>
</tr>
<tr>
<td>Acanthosis</td>
<td>No</td>
<td>Common</td>
</tr>
<tr>
<td>Degree of Hyperglycemia</td>
<td>Variable</td>
<td>Variable</td>
</tr>
<tr>
<td>Ketosis/ketonuria</td>
<td>Common</td>
<td>Mod Common</td>
</tr>
<tr>
<td>Acidosis</td>
<td>Common</td>
<td>25% DKA</td>
</tr>
<tr>
<td>Insulin/C-peptide</td>
<td>Low</td>
<td>Low-High</td>
</tr>
<tr>
<td>Autoimmune Markers</td>
<td>+</td>
<td>20%</td>
</tr>
</tbody>
</table>

**Additional Studies at Diagnosis**

**Lipids:**
- Hyperlipidemia is a common finding in T2DM
- It is the leading cause of mortality in this population
- Screen after glycemic control achieved

**Liver enzymes:**
- 5-10% adults with T2DM have NASH

**Microalbumin**
- True duration of diabetes at time of diagnosis is unknown

**Ophthalmology Evaluation**

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Case Presentation: JS

- Fasting bg = 220
- Fasting bg = 242
Dx: DM
Type 2:
+family hx
AA
obesity
acanthosis

Case Presentation: JS

- BG 220, HCO3 29
- Insulin 37.4 (nl 2.6-24), c-peptide not obtained
- HgA1c= 9.1 (bg= 210), Antibodies neg
- UA with >1000 glucose but neg ketones
- BUN/Creatinine wnl
- Urine for microalbumin/creatinine wnl
- LFTs: AST = 48 and ALT= 72
- Ophthalmology evaluation ordered and wnl

Treatment
Treatment of Prediabetes

- Dietary counseling
- Weight loss
- Physical activity 150min/week
- Follow progress
- Consider metformin if IFG or IGT and:
  - Highest risk of developing DM
  - No progress
- Rescreen for DM every year

Treatment DM: Goals

1) Normalize fasting and post-prandial blood sugars
   - Fasting bg 70-120 mg/dL
   - Post-prandial <180 mg/dL
   - HgA1c ≤ 7%
2) Control associated comorbid conditions
3) Prevent microvascular + macrovascular complications

Aggressive reduction of insulin resistance early in T2DM is beneficial for β cell preservation and prolonged glycemic control.

Keep treatment plan as clear and simple as possible. Frequent follow-up to ensure compliance.

Treatment: Medical Nutritional Therapy

- Cornerstone of treatment for IFG, IGT, and Type 2 DM.
- Develop healthy, sustainable eating habits:
  - Monitor carbohydrate and sodium intakes
  - Limit saturated fat to <7% total calories, limit trans fat
  - Increase fiber (age + 5g/day or 20-25g/d)
- Achieve weight loss (7%)
- 150 minutes of physical activity per week
- If DM, begin metformin
Treatment: Metformin

- FDA approved for children
- First line oral agent
- Mechanism of action:
  - ↓ hepatic gluconeogenesis
  - ↑ muscle insulin sensitivity
  - ↑ liver insulin sensitivity
- Good for fasting hyperglycemia
- May lower HgA1c 1-2%
- No risk hypoglycemia
- Wt stabilizing
- Begin with 500mg at dinner and increase by 500mg a week to 1000mg po bid.
- Monitor fasting blood sugar qd and 2 hour post-dinner a few days a week.
- May help restore ovulation in PCOS
- Good for fasting hyperglycemia
- May lower HgA1c 1-2%
- Wt stabilizing
- Begin with 500mg at dinner and increase by 500mg a week to 1000mg po bid.
- Monitor fasting blood sugar qd and 2 hour post-dinner a few days a week.
- May help restore ovulation in PCOS

Treatment: Metformin

- **Most common side effects:**
  - GI upset (gas, diarrhea, abd pain, nausea, vomiting)
  - Resolves in 2 weeks of therapy
  - Less likely to occur if initial dose is low 500mg po bid and dose is taken with food
  - Recommended dose is 1000mg po bid
- **Megaloblastic Anemia**
  - Interferes with B12 absorption

Treatment: Metformin

- **Lactic Acidosis**
  - Rare (1/30,000 patient years) but serious complication of metformin use
  - Need to document that patient counseled
  - Malaise, somnolence, myalgias, respiratory distress, abdominal discomfort
- **Contraindicated in:**
  - Renal insufficiency, dehydration, metabolic acidosis, hepatic dysfunction, hemodynamic instability
  - If radiocontrast or surgery, hold for 48 hrs after procedure

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Treatment: Insulin Therapy

- Indicated at diagnosis if:
  Random glucose is > 250 mg/dL
  Symptoms of hyperglycemia
  Ketosis or ketoacidosis
  HgA1c ≥ 10

- Indicated as adjunctive therapy to metformin if:
  Lifestyle and metformin maximized
  HgA1c >8

- Associated with: hypoglycemia and weight gain
- Type of insulin used depends on patient and practitioner

Risk factors and markers:
1) Minority population
2) Family hx T2DM
3) IUGR - 2-7fold increased risk T2DM
4) Obesity
5) Puberty - increased growth hormone

Glucotoxicity
Lipotoxicity
Latent Autoimmunity

Insulin Resistance
Hyperinsulinemia
- Normal glucose tolerance
- Postprandial hyperglycemia

β-cell Dysfunction
- Impaired first-phase insulin response
- Post-prandial hyperglycemia

Type2DM
- Insulin Resistance
- Hepatic gluc production

Treatment: Insulin Therapy

- Indicated at diagnosis if:
  Random glucose is > 250 mg/dL
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- Type of insulin used depends on patient and practitioner

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**Treatment: Insulin Therapy**

- Lantus 10 units qhs with plan to increase by 2 units q 2 days to goal fasting bg <120
- May try 0.1–0.25U/kg/day
- Education on:
  - Hypoglycemia symptoms
  - Glucagon use
  - Exercise and DM
  - Need for medical alert
  - Sick day management
- Will need meal coverage if HgA1c > 8

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**Treatment: Other Pharmacologic Agents**

- **Aims of therapy:**
  - 1) Increase insulin sensitivity
  - 2) Increase insulin secretion
  - 3) Slow post-prandial glucose absorption

- **Drug Classes:**
  - 1) Sulfonylureas
  - 2) Meglitinides
  - 3) Thiazolidinediones
  - 4) Incretin mimetics
  - 5) Dipeptidyl-peptidase-4 inhibitors
  - 6) α glucosidase inhibitors

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**Treatment: Sulfonylureas**

- Not FDA approved for adolescents
- Used as adjunctive therapy to Metformin if HgA1c remains↑
- Mechanism of action
  - Increases insulin secretion
- Taken bid 30 min prior to meals
- Good for post-prandial hyperglycemia
- May lower HgA1c 1-2%
- Side effects include:
  - Hypoglycemia
  - Weight gain
- Meglitinides also lower glucose by binding to the sulfonylurea receptor.
Treatment: Thiazolidinediones (TZDs)

- Not FDA approved for adolescents
- Used as adjunctive therapy to metformin
- Mechanism of action:
  - Activates a nuclear receptor
  - Peroxisome Proliferator Activated Receptor
  - Increased insulin sensitivity
- Good for fasting hyperglycemia
- No risk hypoglycemia
- May lower HgA1c 1-1.5%
- Side effects include:
  - Edema, wt gain
  - ?↑ bone fracture rate
  - May take 6+ weeks to see benefit

Incretins: Glucagon-Like Peptide 1

- Incretins are gut derived peptides that are normally secreted in response to a meal.
- GLP-1 is the most widely studied incretin.

- GLP-1 acts to:
  1) Stimulate insulin release from pancreatic β cells in response to glucose
  2) Suppress glucagon release from pancreatic α cells
  3) Slow gastric emptying
  4) Increase satiety

- GLP-1 is typically degraded quickly by dipeptidyl-peptidase-4
Treatment: GLP-1 Agonists

- Not FDA approved for adolescents
- Only available as injection given bid before meals
- Good for controlling post-prandial hyperglycemia
- Can drop HgA1c by 1%
- Promote weight loss!
- Side effects include: Nausea and vomiting
- Increased risk of pancreatitis

Treatment: DPP-4 Inhibitors

- Mechanism of action:
  - Inhibit the enzyme which degrades endogenous incretin hormones.
  - Given po qd, no dose titration
  - May lower HgA1c 0.6-0.8%
  - Reported urticaria, angioedema
  - Risk of pancreatitis
  - Expensive

Treatment: α-Glucosidase Inhibitor

- Taken with carbohydrate containing meals
- Decreases carbohydrate absorption and post-prandial glucose excursions
- Minimal decrease in HgA1c 0.5%
- Side effects: abdominal distention, gas
Management of Co-morbid Conditions

<table>
<thead>
<tr>
<th>HTN:</th>
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<tbody>
<tr>
<td>Increases risk for renal insufficiency, retinopathy, and neuropathy</td>
</tr>
<tr>
<td>Lifestyle modifications when BP 90-95%</td>
</tr>
<tr>
<td>Pharmacological therapy (ace-inhibitor) when BP at or above 95%</td>
</tr>
<tr>
<td>Hyperlipidemia:</td>
</tr>
<tr>
<td>Goal is:</td>
</tr>
<tr>
<td>LDL &lt;100mg/dL</td>
</tr>
<tr>
<td>HDL &gt;35mg/dL</td>
</tr>
<tr>
<td>TG &lt; 150mg/dL</td>
</tr>
<tr>
<td>Consider statin therapy if LDL 130-159mg/dL</td>
</tr>
<tr>
<td>Initiate therapy if LDL ≥ 160mg/dL</td>
</tr>
</tbody>
</table>

Management of Co-morbid Conditions

| Depression |
| Sleep apnea |
| PCOS |

Type 2 DM: Follow-up

| Close follow-up needed because compliance can be more of an issue than in Type 1. |
| Nutrition therapy |
| Clinic visit q 3 months: |
| – Follow wt, BMI, BP |
| – Exercise routine and diet |
| – Blood sugar log, HgA1c |
| Annual labs to include: LFTs, lipids, TFTs, microalbumin |
| Dilated eye exam annually |
| Influenza vaccine |
| Psychology services |
| Diabetes education: sick day management |

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Hyperglycemic Hyperosmolar Syndrome (HHS)

**HHS**

- Incidence ↑ in pediatric T2DM
- Obese, AA males
- Present at diagnosis (4%) or can develop during illness/non-compliance
- Case fatality rate of 12%
- **Symptoms:**
  - Polyuria, polydipsia, nocturia
  - Abd pain, nausea, vomiting
  - HA, lethargy
  - Wt loss

<table>
<thead>
<tr>
<th>Diagnostic criteria:</th>
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<tbody>
<tr>
<td>Glucose &gt;600mg/dL</td>
</tr>
<tr>
<td>Serum osm &gt;330mOsm/kg</td>
</tr>
<tr>
<td>Lack of significant acidosis</td>
</tr>
<tr>
<td>HCO3&gt;15</td>
</tr>
<tr>
<td>Lack of significant ketosis</td>
</tr>
</tbody>
</table>

**HHS: Pathophysiology**

- Relative insulin deficiency/stress
- Hyperglycemic hyperosmolar state
- No lipolysis or ketogenesis
- Prolonged polyuria leads to severe dehydration and electrolyte losses (↓K, ↓Phos, ↓Mg)
- Hypertonicity of ECF may mask signs of hypovolemia
- Acidosis is typically due to poor perfusion, lactic acidosis

HHS: Treatment

- **Restore intravascular volume**
- **Bolus 20cc/kg NS at dx**
- **Assume 12-15% fluid down**
- **Replace over 24-48hrs with 0.45% to 0.75% NS**
- **20 KCl and 20 KPhos**
- **Replace UO q 2hrs**
- **Gradual correction of:**
  - Osmolality
  - Hyperglycemia (<75-100mg/dL/hr)
  - Hypernatremia (<0.5mEq/L/hr)
- **Fluid therapy corrects hyperglycemia**
  - Dilution
  - Increased renal perfusion
  - Increased tissue perfusion
- **Insulin therapy not critical initially**

HHS: Treatment

- **Insulin therapy may be dangerous**
- **Worsen intravascular volume**
- **Worsen hypokalemia**
- **Insulin therapy should be considered if glucose no longer dropping with fluids alone.**

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HHS: Treatment

Complications:
- Vascular collapse
- Hypokalemia and arrhythmia
- Hypophosphatemia and rhabdomyolysis
- Intravascular thrombosis
- Malignant hyperthermia-like syndrome
- Pancreatitis
- Mental status changes
  - Cerebral edema much less common than in DKA

Monitor:
- Hourly glucose and vital signs
- Q2hrs CMP, Osmolality, fluid balance, CK
- Q4hrs Ca, Phos, Mg
- Continuous cardiac monitor

Summary

- T2DM now accounts for 8-45% of all new pediatric and adolescent cases of diabetes.
- Most patients are asymptomatic at diagnosis.
- It is critical to be familiar with ADA screening guidelines.
- Once diagnosis is made, test for micro and macrovascular complications.
- Treatment involves: lifestyle modification, nutrition therapy, oral hypoglycemic agents, insulin, management of co-morbidities.
- Keep treatment plan simple and follow-up frequent.
- Patient can present in HHS or can develop HHS when ill / non-compliant

References

Antibodies and T2DM

- Found in 10-20% of adults with presumed T2DM
- Explained by the “accelerator hypothesis”:
  Insulin resistance -> hyperglycemia -> glucose toxicity ->
  Beta cell apoptosis with development of β cell autoimmunity
- Antibodies indicate:
  - Earlier need for insulin therapy (esp GAD)
  - Concern for other autoimmune illnesses (TFTS, celiac)

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