Contemporary Issues in Diabetes

Type 2 Diabetes in Adolescents

Type 2 Diabetes in Adolescents

- In the past, Type 1 DM was the only type of diabetes that was observed in children...
  - Only 1-2% considered to have Type 2
- Over the last 20 years, 8-45% of children diagnosed with diabetes have Type 2
- Why this increase?
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Type 2 Diabetes in Adolescents – Why?

- Increase incidence of obesity
  - Prevalence of overweight adolescents

Type 2 Diabetes in Adolescents

- Clinical presentation of Type 1 and Type 2 diabetes may be indistinguishable
  - Important to classify DM correctly for management

<table>
<thead>
<tr>
<th></th>
<th>Type 1</th>
<th>Type 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obesity</td>
<td>1/4</td>
<td>Majority</td>
</tr>
<tr>
<td>Ketosis</td>
<td>+</td>
<td>+ in 1/3</td>
</tr>
<tr>
<td>Family Hx</td>
<td>5%</td>
<td>74-100%</td>
</tr>
<tr>
<td>Weight loss</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>C-peptide</td>
<td>↓</td>
<td>&gt; or ↑</td>
</tr>
<tr>
<td>B-cell auto-Ab</td>
<td>+</td>
<td>-</td>
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</tbody>
</table>

Type 2 Diabetes in Adolescents – Why?

- Decreased physical activity
- Increased overeating
- Pathophysiology is similar to adult Type 2 DM
  - Hyperinsulinemia
  - Insulin resistance
  - Inadequate insulin secretion
- Tend to have a strong family history of Type 2 DM

Who should be screened for Type 2 DM ...

- Overweight adolescents (≥ 10 yo or onset of puberty) AND the presence of any 2 of the following...
  - Family history of Type 2 DM in a first- or second-degree relative
  - Race: Native American, African American, Hispanic, Asians, or Pacific islanders
  - Signs of insulin resistance – acanthosis nigricans, HTN, dyslipidemia, or polycystic ovary syndrome
  - Maternal history of DM or GDM
- Fasting glucose - every 2 years
- Conformational test needed for diagnosis
**Type 2 Diabetes in Adolescents**

- **Management**
  - Goal: normalization of blood glucose and HbA1c and reduce the risk of diabetic complications
  - Control other comorbidities
    - Treat BP or dyslipidemia
    - Quit smoking
  - Self-management education
  - Diet and physical activity → weight loss
  - Medication management
    - At some point, most will require drug therapy
    - Oral agents offer better adherence and convenience vs. insulin therapy

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**Type 2 Diabetes in Adolescents**

- **Medication Management**
  - For those who are not acutely ill
    - Metformin – first-line
      - No risk of hypoglycemia
      - No weight gain
      - Positive effects on lipid parameters
      - Maximum dose in adolescence = 2000mg/d
    - Second-line
      - Consider Sulfonylureas or insulin
    - Others – can use, but not studied as well
      - Glinides
      - Alpha-glucosidase inhibitors
      - TZDs?

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**Management – (ctnd.)**

- Prevention of complications
  - Microvascular
    - Retinopathy – yearly ophthalmologic exams
    - Nephropathy – yearly screening for microalbuminuria
  - Neuropathy – daily self-check, yearly physician exam
  - Macrovascular
    - Control BP, dyslipidemia
    - Stop smoking
    - Lose weight
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**Type 2 Diabetes in Adolescents**

- More studies needed...
  - Risk factors to identify ‘at-risk’ adolescents
  - Efficacy and safety of oral agents compared to insulin
  - Risk of diabetic complications and prevention strategies

**Question?**

What is the preferred first line drug treatment for most adolescents with type 2 diabetes?

- a. Glipizide
- b. Metformin
- c. Acarbose
- d. Pioglitazone

Please type your answer in the chat box

**Pre-Diabetes**

- Definition...
  - Impaired Fasting Glucose (IFG)
    - Fasting blood glucose of 100-125 mg/dl
  - Impaired Glucose Tolerance (IGT)
    - OGTT with 2hr blood glucose of 140-199 mg/dl

- Increased risk of developing...
  - Cardiovascular disease
  - Type 2 DM

**Pre-Diabetes**

- 10 y incidence rate of diabetes (%)

<table>
<thead>
<tr>
<th>IFG</th>
<th>BMI</th>
<th>FBS</th>
<th>HDL</th>
<th>BP</th>
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</thead>
<tbody>
<tr>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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Pre-Diabetes

- Risk of diabetes over 5-6 years...
  - Normal IFG or IGT – 4 - 5%
  - IFG only OR IGT only – 20 - 34%
  - IFG + IGT – 38 - 65%

- Incidence of pre-diabetes in the U.S.
  - Estimated at 25% of overweight adults aged 45-74 yrs OR 12 million adults

Pre-Diabetes – The Evidence...

- Diet and Exercise
  - Intensive diet + exercise counseling for at least 2 yrs
    - Goals: 5-7% weight loss + exercise (150 min/wk)
    - Average weight loss of 4.6 to 12.3 lbs
    - Progression to diabetes was reduced by 58% with intensive diet and exercise
    - Diet and exercise works for ALL individuals

Pre-Diabetes

- Usually found...
  - On routine screening for Type 2 DM
  - After evaluation for insulin resistance due to the presence of other risk factors

- What do you do after you find pre-diabetes?

Pre-Diabetes – The Evidence...

- Metformin
  - Dose studied: 850 mg BID for ~3 yrs
  - Average weight loss was 4.6 lbs.
  - Progression to diabetes was reduced by 31%
  - Metformin was most effective in younger, obese individuals
  - Diet and exercise was SUPERIOR to metformin
Pre-Diabetes – The Evidence...

- Thiazolidinediones
  - Rosiglitazone (8 mg QD) – DREAM study
    - Found to reduce the progression of DM by 60% after 3 yrs
    - Found to reduce BP
    - Increase in CHF events and weight vs. PBO
  - Pioglitazone (45mg QD)
    - Found to reduce the progression of DM by 81% over 2.6 yrs
    - Increase weight vs. PBO

- Alpha-glucosidase inhibitors – Acarbose
  - Dose studied: 100mg TID prior to meals for ~ 3 years
  - Progression to diabetes was reduced by 25%
  - Post-hoc analysis: acarbose reduced the risk of a CV event by 49% and developing HTN by 34%
    - 72% of CV events were in patients with IGT

- Other options
  - Orlistat study
    - 37% reduction in the progression to DM in patients with IGT after 4 yrs
    - More normalization their glucose levels in patients with IGT at baseline
  - ACEI studies - reduced incidence of new-onset DM by...
    - 14% with captopril; 34% with ramipril; 25% with lisinopril
    - Positive findings were found in sub-group analyses of unrelated trials
    - Prospective trials have not shown same benefit
  - ARB studies - reduced incidence of new-onset DM by...
    - 25% with losartan
    - 20% with valsartan

Pre-Diabetes – Management

- Recommendations
  - Weight loss
    - Indicated for all overweight or obese patients (BMI ≥ 30 kg/m^2) with pre-diabetes
      - 5-10% (~7%) of body weight
    - Low-calorie diet + physical activity (at least 30 minutes daily or 150 min/wk)
Pre-Diabetes – Management

- Recommendations – (ctnd.)
  - Pharmacologic therapy
    - Little information on the benefit of any therapy in preventing CV disease in patients with pre-diabetes
    - “…insufficient evidence to support the use of drug therapy as a substitute for, or routinely used in addition to, lifestyle modification to prevent diabetes.”
    - Consider **metformin** for individuals at VERY HIGH risk
      - IFG and IGT plus other risk factors (i.e., A1C 6%, HTN, low HDL, high TG, or FH of DM) and who are obese and < 60yo
  - Monitor for the progression to Type 2 diabetes every year

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Pre-Diabetes

- More studies needed…
  - Drug therapy effect on prevention of microvascular and CV disease
  - Cost-effectiveness of using drug therapy
  - Ways to sustain weight loss and dietary and exercise changes
  - Ways to effectively implement diet and exercise in high risk patients
  - Most effective ways to identify patients with pre-diabetes

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Pre-Diabetes - Case

MM is a 63 yo white female with hypertension, hypertriglyceridemia, GERD and osteoarthritis

**Medications:**
- HCTZ 25 mg QD
- Lisinopril 40 mg QD
- Toprol XL 50 mg QD
- Tricor 145 mg QD
- Prevacid 30 mg QD
- Celebrex 200 mg QD

**Vitals and Labs:**

<table>
<thead>
<tr>
<th>Date</th>
<th>FBG</th>
<th>BP</th>
<th>Weight</th>
<th>Height</th>
<th>BMI</th>
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<tbody>
<tr>
<td>6/7/09</td>
<td>108</td>
<td>150/80</td>
<td>233</td>
<td>60 in.</td>
<td>45</td>
</tr>
<tr>
<td>9/8/08</td>
<td>132/80</td>
<td>232</td>
<td>45</td>
<td></td>
<td></td>
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</tbody>
</table>

**Lipid profile:**
- TG 180
- HDL 42
- LDL 76
- VLDL 26

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Pre-Diabetes - Case

- Does she have pre-diabetes?
- How would you manage MM?
- How would you monitor MM?
Definition

- The presence of multiple metabolic risk factors that are commonly found together and are associated with an increased risk of cardiovascular disease (CVD)

Other synonyms...

- Syndrome X
- Insulin resistance syndrome

Components...

- Abdominal obesity
- Insulin resistance ± glucose intolerance
- Atherogenic dyslipidemia
- Elevated blood pressure
- Proinflammatory state
- Prothrombotic state

Metabolic syndrome is estimated to affect 33.7% of men and 35.4% of women

- Prevalence increases with age with 43.5% over 65 yrs of age likely to be affected
- ⅓ of overweight/obese patients meet criteria for metabolic syndrome

- Predicts 25% of all new cases of CVD and associated with a 3-times increased risk of CVD

- Highly predictive of new-onset diabetes

Obesity

- Associated with a higher risk of CVD
- Contributes to HTN, increased cholesterol, low HDL, and hyperglycemia
- Abdominal obesity (visceral adipose tissue – VAT)
  - Higher rate of lipolysis and increased FFA production
  - FFA stimulate production VLDL and decrease insulin sensitivity in peripheral tissues
  - Adipose tissue releases cytokines that also decrease insulin sensitivity
  - Leads to atherogenic dyslipidemia and insulin resistance
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Insulin resistance and hyperinsulinemia
- Insulin resistance increases with increasing BMI
- Promotes fatty liver and development of atherogenic dyslipidemia
- Associated with a proinflammatory state
- May raise BP by a variety of mechanisms

Atherogenic dyslipidemia and increased blood pressure
- Can result from obesity and insulin resistance, but is strongly influenced by genetics and dietary factors
- Overall...
  - Pathogenesis is complex and, likely, multifactorial... more research is needed

What is atherogenic dyslipidemia?
- Hypertriglyceridemia
- Increased apolipoprotein B
- Increased small, dense LDL particles
- Reduced HDL

Presence of 3 of the following...
- Abdominal obesity - waist circumference
  - M - > 40 inches (102 cm)
  - F - > 35 inches (88 cm)
- TG ≥ 150 mg/dL
- HDL
  - M - < 40 mg/dL
  - F - < 50 mg/dL
- SBP ≥ 130 or DBP ≥ 85 mmHg
- Fasting glucose ≥ 100 mg/dL
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**Metabolic Syndrome - Management**

- Manage risk factors!!
- Primary intervention – Weight Reduction
  - Low calorie diet
  - Low fat with reduced sugar consumption and increased fruits, vegetables and whole grains
  - Increase physical activity
  - Work up to a minimum of 30 minutes of moderate-intensity physical activity on a daily basis
  - Improves dyslipidemia, lowers BP, lowers glucose and insulin resistance, decreases C-reactive protein and PAI-1
  - Goal = 5-10% loss of body weight in 1st year

If insulin resistance is present...
- Metformin
  - Found to prevent or delay development of Type 2 diabetes in patients with pre-diabetes
- Thiazolidinediones (TZD)
  - Shown to improve insulin resistance, reduce BP and CRP in patients with metabolic syndrome
  - Effect on lipids
    - Rosiglitazone: ↑ LDL (23%), ↑ HDL (8%), ↑ TG (14%)
    - Pioglitazone: ↓ LDL, ↑ HDL (15%), ↓ TG (12%)
  - No studies showing a reduction in CVD end-points for metabolic syndrome

If atherogenic dyslipidemia present...
- Goals: LDL < 100, TG < 150, HDL > 40 (♂) or 50 (♀)
- Statins
  - Subgroup analyses found statins reduce risk of CVD in patients with metabolic syndrome
- Fibrates – gemfibrozil and fenofibrate (TriCor)
  - Improve all components of atherogenic dyslipidemia
  - Analyses of trials found fibrates reduce risk of CVD in patients with metabolic syndrome
- Niacin
  - Studies suggest a statin-fibrate combination improves the lipid profile over either agent alone

If elevated BP present...
- Goal BP < 130/80 (DM) or < 140/90 (no DM)
- Preferred agents: ACEI or ARB

If elevated CRP (≥ 3 mg/L) present...
- Lifestyle modifications, consider statin therapy
- Prothrombotic state??
  - PAI-1
  - Initiate low-dose aspirin
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Metabolic Syndrome – Remaining Questions???

- Need to improve recognition of people with metabolic syndrome
- More studies needed...
  - Impact of insulin sensitizers (metformin and TZDs)
  - Impact of treating atherogenic dyslipidemia
  - Ideal BP-lowering agent
  - Impact of treating elevated CRP
  - Ways to target prothrombotic state
  - Most effective ways to identify patients with metabolic syndrome
  - Management strategies that improve the CVD risk!!

Metabolic Syndrome – Case

BP is a 57 yo white female with asthma, sleep apnea, hypothyroidism, hypertension, recurrent PE with protein C and S deficiency, and paroxysmal atrial fibrillation

Family history: ฿ for DM (father)

Social history: ฿ smoking

Vital signs: wt. 360 lbs, ht. 67 in., BMI 56.5

Labs:

8/20/09: FBG 118, BP 132/88
6/10/09: TC 184, LDL 91, HDL 46, TG 236

Does she have metabolic syndrome?

- Abdominal obesity
- Insulin resistance ± glucose intolerance
- Atherogenic dyslipidemia
- Elevated blood pressure
- Pro-inflammatory state
- Pro-thrombotic state

Management

- Abdominal obesity
  - Weight reduction – 5-10% weight loss

- Insulin resistance
  - Weight reduction
  - Pharmacologic therapy
    - Metformin?
    - TZD?
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Management

- Atherogenic dyslipidemia
  - Statins vs. fibrates
- Blood pressure
  - Pharmacologic therapy
    - Was on Norvasc 2.5 mg OD
    - Other agents to consider?

- Pro-inflammatory state
  - Measure CRP
  - If ≥ 3 mg/dL, consider statin therapy
- Pro-thrombotic state
  - On warfarin for recurrent PE