Type 2 Diabetes in Youth
(and other complications of obesity)

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Disclosures

• Dr. Styne will mention medications that are not approved for children
• Dr. Styne has no financial interest in any treatments mentioned
Objectives
At the Conclusion of This Session The Participant Will Be Able to:

• Understand the Etiology of Type 2 Diabetes Mellitus
• Understand the Epidemiology of Type 2 Diabetes
• Understand the Diagnosis of Type 2 Diabetes
• Understand the Treatment of Diabetes
Type 2 Diabetes in Youth (and other complications of obesity)

- The Problem
- The Cause
- The Diagnosis
- The Treatment
  - T2DM
  - Nephropathy
  - Hypertension
  - Dyslipidemia
First Notice?

7-14 Years Old

CLINICAL AND COMMUNITY STUDIES
ÉTUDES CLINIQUES ET COMMUNAUTAIRES

Non-insulin-dependent diabetes mellitus in Indian children in Manitoba

CAN MED ASSOC J 1992; 147 (1)
A Pending Epidemic?
Type 2 (Adult Onset) Diabetes Mellitus During Childhood

- Recognized in Native American children in first
- A 10 fold increase noted by 1995 in Cincinnati
- Found internationally where obesity increases
- Presently 8-45% of new DM
- 2006: T2 DM prevalence estimates 1.54 / 1000
- By 2030, type 2 predicted to be more common than type 1 diabetes in youth
- Probably will cause early kidney, eye and cardiac disease based upon results of young adult onset
Age-Adjusted Prevalence of Diagnosed Diabetes Among U.S. Adults

2005

Prevalence of Diabetes in U.S. Youth in 2009: The SEARCH for Diabetes in Youth Study


Diabetes Care 37(2): 402-408.
Prevalence of Diabetes in U.S. Youth in 2009: The SEARCH for Diabetes in Youth Study

Diabetes Care 37(2): 402-408.
Obesity and type 2 diabetes mellitus in a birth cohort of First Nation children born to mothers with pediatric-onset type 2 diabetes

- Historical evidence indicates that the Oji-Cree people did not have diabetes before colonization and at the beginning of the 20th century.
- As of April 2008, 7/28 (25%) of the offspring aged 7–19 years have diabetes including 6/14 (43%) aged 10–19 years. All of the 7 offspring with diabetes have 1 or 2 copies of the G319S polymorphism.
- Conclusions: The prevalence of type 2 diabetes in this cohort of offspring of First Nation women with pediatric-onset type 2 diabetes is the highest ever reported.

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  - Dyslipidemia
Type 2 Diabetes Requires Insulin Resistance and Relative Insulin Deficiency
When Do We Suspect Diabetes?

• Classic polyuria, polydipsia
• Unexplained and unplanned weight loss
• Obesity (BMI > 95th%) in the Teen Years
• Overweight (BMI 85-95%) with risk factors
  – Family History
  – Acanthosis Nigricans
  – Other Signs or Symptoms of Insulin Resistance
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  - Dyslipidemia
### The Diagnosis of Diabetes Mellitus

Glucose tolerance test after 1.75 gm/kg carbohydrate load
(75 grams maximum)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Fasting BS</th>
<th>1 Hour BS</th>
<th>2 Hour BS</th>
<th>3 Hour BS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Normal BS</strong></td>
<td>&lt;100</td>
<td>&lt;200</td>
<td>&lt;140</td>
<td>&lt;130</td>
</tr>
<tr>
<td>Insulin (mu/ml)</td>
<td>9</td>
<td>51</td>
<td>37</td>
<td>20</td>
</tr>
<tr>
<td>C-peptide ng/ml</td>
<td>1.3</td>
<td>3.3</td>
<td>3.0</td>
<td>2.0</td>
</tr>
<tr>
<td><strong>Impaired Glucose Tolerance (IGT)</strong></td>
<td>101-125</td>
<td>140-199</td>
<td>130-199</td>
<td></td>
</tr>
<tr>
<td><strong>Diabetes Mellitus (DM)</strong></td>
<td>&gt;126</td>
<td>&gt;200</td>
<td>&gt;200</td>
<td>&gt;200</td>
</tr>
</tbody>
</table>
Diagnostic Criteria for Diabetes and Pre-Diabetes

- **Normal Glucose Tolerance**
  - Fasting Glucose: 199 mg/dL
  - 2-Hour Post-Prandial Glucose: 140 mg/dL

- **IGT** (Impaired Glucose Tolerance)
  - Fasting Glucose: 100 mg/dL
  - 2-Hour Post-Prandial Glucose: 199 mg/dL
  - A1c: 5.7-6.4%

- **IFG** (Impaired Fasting Glucose)
  - Fasting Glucose: 125 mg/dL
  - A1c: 5.7-6.4%

- **DIABETES**
  - A1c: ≥6.5%

Courtesy of Dr. Janet Silverstein
IGF, IGT in Adolescents 12-19 years old
NHANES 2005-2006

<table>
<thead>
<tr>
<th>IGF</th>
<th>IGT</th>
<th>Pre-Diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>13.1%</td>
<td>3.4%</td>
<td>16.1%</td>
</tr>
</tbody>
</table>

Predictors of Pre-Diabetes

- Overweight sibling of child with T2DM
  - 40% of OW (>95% BMI) sibs vs 14% OW controls without a T2DM sib had abnormal IGT*

- 2 of the following cardiometabolic risk factors:
  - Central obesity
  - TG> 150 mg/dL
  - HDL-C< 40 mg/dL
  - HTN

- Infant of a mother with diabetes during pregnancy

Testing for Type 2 Diabetes in Children

- **Criteria**: Overweight (BMI > 85th %ile for age and sex, wt for ht > 85th %ile, or wt > 120% of ideal for ht)

  PLUS: any two of the following risk factors:
  - Family history of DM 2 in 1st or 2nd degree relative
  - Race/Ethnicity
  - Signs of insulin resistance

- **Age of Initiation**: age 10 or at onset of puberty
- **Frequency**: every two years
- **Test**: Fasting plasma glucose preferred

*Clinical judgment should be used to test for diabetes in high risk patients who do not meet these criteria.*

ADA/AAP Recommendations, Diabetes Care 23:2000
When Should we do a Glucose Tolerance Test in Childhood?

• **Probably Never in Strongly Suspected 2 Diabetes**
  - Fasting Hyperglycemia (>126 mg/dl) or casual BG (>200mg/dl) with Polyuria and Polydipsia and Weight Loss:
    - Even Obese Children Can Get Type 1 Diabetes Mellitus!

• **Differentiate Type 1 from Type 2 in Difficult Cases?**
  - Extremely difficult in the early “honeymoon” period
  - Antibody levels might help but not infallible
  - Two hour post prandial vs. oral glucose tolerance test after CH2O loading
  - C peptide determination, especially if insulin already administered
PREVALENCE OF IMPAIRED GLUCOSE TOLERANCE AMONG CHILDREN AND ADOLESCENTS WITH MARKED OBESITY

Obese Preadolescents

76% Normal Glucose Tolerance (NGT)

24% Impaired Glucose Tolerance (IGT)

Obese Adolescents

76% Normal Glucose Tolerance

20% Impaired Glucose Tolerance (IGT)

4% Silent Type 2 Diabetes

RANJANA SINHA, M.D., GENE FISCH, PH.D., BARBARA TEAGUE, R.N., WILLIAM V. TAMBORLANE, M.D., BRUNA BANYAS, R.N., KARIN ALLEN, R.N., MARY SAVOYE, R.D., VERA RIEGER, M.D., SARA TAKSALI, M.P.H., GINA BARBETTA, R.D., ROBERT S. SHERWIN, M.D., AND SONIA CAPRIO, M.D.

(N Engl J Med 2002;346:802-10.)
Progression from Pre-Diabetes to Diabetes in Adolescents

Progression from Pre-Diabetes to Diabetes in Adolescents

- Progressors and non-progressors had
  - same pubertal status and same age
  - same insulin sensitivity
  - significant slightly higher BG values in progressors
  - significantly lower β cell function in progressors

- At 30 months:
  - Si and β cell function deteriorated in progressors but stayed unchanged in non-progressors

- Cali AMG, et. al. Diabetes Care 32(3):456-461; Mar 2009
Type 2 Diabetes in Youth (and other complications of obesity)

• The Problem
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• The Treatment
  – T2DM
  – Nephropathy
  – Hypertension
  – Dyslipidemia
<table>
<thead>
<tr>
<th></th>
<th>Type 1</th>
<th>Type 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not usually overweight</td>
<td>Proportionate to obesity in general population</td>
<td>85% are overweight</td>
</tr>
<tr>
<td>Short course</td>
<td>Indolent Course</td>
<td></td>
</tr>
<tr>
<td>35-40% present with ketoacidosis</td>
<td></td>
<td>33% with ketonuria</td>
</tr>
<tr>
<td>5% with a 1st or 2nd degree relative with type 1</td>
<td></td>
<td>5-25% may have ketoacidosis</td>
</tr>
<tr>
<td>Increased incidence of other autoimmune d/o: thyroid; adrenal; vitiligo; celiac. + antibodies</td>
<td></td>
<td>Increase in PCOS Acanthosis nigricans (in up to 90%) Increase in hypertension</td>
</tr>
<tr>
<td>Decreased C-peptide &amp; Insulin No increase with glu challenge</td>
<td></td>
<td>Nl or increased C-P &amp; Insulin Increase with glucose challenge</td>
</tr>
<tr>
<td>Caucasians predominate</td>
<td></td>
<td>NA; AA; Latino; Asian; Pacific Islander</td>
</tr>
</tbody>
</table>
## Differences in Management Between T1DM and T2DM

<table>
<thead>
<tr>
<th>Type 1 DM</th>
<th>Type 2 DM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin is mainstay of treatment</td>
<td>Lifestyle modification is key treatment</td>
</tr>
<tr>
<td>Lifelong insulin needed</td>
<td>May not need insulin for first several years</td>
</tr>
<tr>
<td>Monitor for complications after 10 yo and 3-5 yrs DM</td>
<td>Monitor for complications at DM onset</td>
</tr>
</tbody>
</table>
Lifestyle Trumps Medication

LifeStyle Improves NAFLD

Clinicians encourage youth with T2DM to

• Engage in moderate-to-vigorous exercise for at least 60 minutes daily

• Limit non-academic screen time to less than 2 hours a day.
What Did we Learn from the DCCT?

• Good control will forestall the complications of Type 1 Diabetes Mellitus
  – Retinopathy Development reduced by 76%
  – Retinopathy Progression reduced by 61%
  – Microalbuminuria development reduced by 56%
  – Neuropathy (adults) reduced by 60%

• Good control will increase the likelihood of hypoglycemic episodes

• Good control will best be achieved by the use of the team approach: Doctor, Nurse-educator, Dietician, Social Worker: this is the state of the art for therapy

• These findings probably will apply to Type 2 Diabetes Mellitus
AAP Key Action Statements

• Clinicians must ensure that insulin therapy is initiated for children and adolescents with T2DM
  – who are ketotic or in diabetic ketoacidosis
  – who have venous or plasma blood glucose levels \( \geq 250 \text{ mg/dl} \)
  – whose Hemoglobin A1c is \( > 9 \) percent; or
  – in whom the distinction between Type 1 and Type 2 diabetes is unclear.
AAP Key Action Statements

In all other instances, clinicians should start metformin as first-line therapy for children and adolescents at the time of diagnosis with T2DM, and initiate a lifestyle modification program including nutrition and physical activity.
AAP Key Action Statements

• Clinicians should monitor Hemoglobin A1c (A1c) levels every three months and intensify treatment if treatment goals for BG and A1c levels are not being met.
• A biological lie detector!
AAP Key Action Statements

• Advise patients to monitor finger-stick BG levels in those who:
  – are taking insulin or other medications with a risk of hypoglycemia; or
  – are initiating or changing their diabetes treatment regimen; or
  – have not met treatment goals; or
  – have intercurrent illnesses.
## Initial Treatment of Blood Glucose

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Blood Glucose</th>
<th>Ketones</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>&lt;250</td>
<td>Negative</td>
<td>Metformin</td>
</tr>
<tr>
<td>No</td>
<td>&gt;250</td>
<td>Negative</td>
<td>Insulin ± Oral agents</td>
</tr>
<tr>
<td>Yes</td>
<td>&gt;200s</td>
<td>Negative</td>
<td>Insulin</td>
</tr>
<tr>
<td>Yes</td>
<td>&gt;200s</td>
<td>Positive</td>
<td>Insulin</td>
</tr>
</tbody>
</table>
**Major Classes of Oral Medications**

1. Drugs that sensitize the tissues to insulin and/or control hepatic glucose production
   - Thiazolidinediones***
   - Biguanides+++  

2. Drugs that stimulate beta-cell insulin production
   - Sulfonylureas
   - Meglitinides (short acting)

3. Drugs that slow the absorption of starches
   - Alpha-glucosidase inhibitors

4. Drugs that increase GLP-1
   - Exenatide (injection!)
   - DPP-4 Inhibitors
## Glycemic Targets*

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Normal</th>
<th>Reasonable Goals</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fasting (or Preprandial) Glucose</strong></td>
<td>&lt;100</td>
<td>70-130</td>
</tr>
<tr>
<td><strong>Postprandial Glucose</strong></td>
<td>&lt;140</td>
<td>&lt;180</td>
</tr>
<tr>
<td><strong>Bedtime BG</strong></td>
<td>&lt;120</td>
<td>90-150</td>
</tr>
<tr>
<td><strong>HbA&lt;sub&gt;1c&lt;/sub&gt; (DCCT Method)</strong></td>
<td>&lt;6%</td>
<td>&lt;7%</td>
</tr>
</tbody>
</table>

Glucose values are plasma (mg/mL).

*Combined WHO recommendations and ADA guidelines.
Because T2DM is but 1 comorbid condition of MS, tx must address all other co-morbidities.
Prevalence of Cardiovascular Risk Factors and Metabolic Syndrome in Youth with Type 2 DM

Mayer-Davis 2008
Complications Occur Early in T2DM in ADOLESCENTS

Frequency Within 1.3 Years of DM Onset

- Microalbuminuria 28%
  (7% at 3 mos)
- Hypertension 36%

Mean A1c 7.3%........thus, not due to poor glucose control

Treatment Goals

- **Weight reduction**
  - decreases insulin resistance
- **Normoglycemia and normal HbA1c**
  - decreases microvascular disease
- **Control co-morbidities of insulin resistance, the most important contributors to macrovascular disease**
  - Hypertension
  - Dyslipidemia
  - Acanthosis
  - Hyperandrogenism: PCOS and hirsutism
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Microalbuminuria

- Normal <30 mg/gm creat on spot urine
- Represents inflammatory state of vessels
- Increased in white coat HTN and non-dippers
- Obtain 2 additional urine samples at least 1 month apart over the next 3-6 months
  - Ideally with first morning void
- If all 3 abnormal, treat with ACE-I
Micro to Macroalbuminuria

• Elevated albuminuria is infrequent and largely transient in nondiabetic youth, but is relatively frequent and largely persistent in those with diabetes. Microalbuminuria in youth with type 2 diabetes strongly predicts progression to macroalbuminuria, supporting annual screening for albuminuria.

## Potential Ways To Decrease Risk of Nephropathy


<table>
<thead>
<tr>
<th>Clinical parameter</th>
<th>Intervention</th>
<th>Treatment target</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glycemic control</td>
<td>Lifestyle/Insulin/Metformin</td>
<td>HbA1c ≤ 7%</td>
</tr>
<tr>
<td>Prehypertension (BP &gt; 90th -95th)</td>
<td>Lifestyle</td>
<td>BP &lt; 90th percentile</td>
</tr>
<tr>
<td>Hypertension (BP &gt; 95th percentile)</td>
<td>Lifestyle ± Ace inhibitor or ARB</td>
<td>BP &lt; 90th percentile</td>
</tr>
<tr>
<td>Dyslipidemia LDL ≥2.6mmol/L</td>
<td>Lifestyle</td>
<td>LDL &lt; 2.6mmol/L</td>
</tr>
<tr>
<td>Dyslipidemia LDL &gt;4.1mmol/L</td>
<td>Lifestyle + Statin</td>
<td>LDL &lt; 2.6mmol/L</td>
</tr>
<tr>
<td>Overweight/Obesity</td>
<td>Lifestyle</td>
<td>BMI &lt; 85th percentile</td>
</tr>
<tr>
<td>Smoking</td>
<td>Cessation tools</td>
<td>Discontinue smoking</td>
</tr>
</tbody>
</table>
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  - Dyslipidemia
Hypertension in Childhood Obesity

• Measure it right
  – Correct cuff
    • May be enormous
    • Repeat it
• Relate it to height
• Refer to Pediatrics 114:555-576 2004
• Ambulatory BP Urbina et. al. Hypertension 2008;52:433-451 NEW
• Remarkably low cutoffs that may surprise you
Hypertension in Childhood Obesity

- **Life style modification first**
  - Initial treatment: dietary (limit salt) and lifestyle interventions for weight reduction & exercise
  - If BP doesn’t reach target of ≤ 95% for age, gender, height within 3-6 months, treatment with anti-hypertensive agent should be initiated
Hypertension in Childhood

Obesity

• Therapy with “adult drugs”
  – ACE inhibitors particularly in diabetes
    • Anti-hypertensive
    • Anti-thrombotic: inhibits platelet aggregation & endothelin
    • Vasodilation: ↓ production of angiotensin II; ↑ bradykinin levels
    • Limits smooth muscle proliferation & plaque rupture
    • Slows progression of nephropathy & retinopathy

• THEY ARE TERATOGENIC; USE CONTRACEPTION
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Atherosclerosis Starts in Infancy

# Hyperlipidemia in a Fasting Sample

<table>
<thead>
<tr>
<th>Measurement</th>
<th>High</th>
<th>Borderline high</th>
<th>Desirable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol</td>
<td>&gt;=200 mg/dl</td>
<td>170-199</td>
<td>&lt;170</td>
</tr>
<tr>
<td>LDL Cholesterol</td>
<td>&gt;=130</td>
<td>110-129</td>
<td>&lt;110</td>
</tr>
<tr>
<td>HDL Cholesterol</td>
<td>&lt;35 (Low)</td>
<td>35-45</td>
<td>&gt;45</td>
</tr>
<tr>
<td>Triglycerides &lt; 10 years</td>
<td>&gt;=100</td>
<td>75-99</td>
<td>&lt;75</td>
</tr>
<tr>
<td>Triglycerides 10-19 years</td>
<td>&gt;=130</td>
<td>90-129</td>
<td>&lt;90</td>
</tr>
</tbody>
</table>

From Expert Committee NIH 1991
Recommendations for Lipid Treatment: Basic Guidelines

• Treatment should be based on lipid values obtained after diabetes treatment initiated

• **Initial treatment**: diet & exercise if LDL-C >100

• **Pharmacologic rx** should be considered if medical nutrition therapy has failed after 3-6 months, even if chronic hyperglycemia is present
  – Medications should be instituted if LDL is > 160 mg/dl
  – Medication should be considered if LDL is 130-159 based on the child's CVD risk profile
Recommendations for Diet

AHA Step 2 diet

- saturated fat < 7% of calories
- cholesterol < 200 mg/day
- For children and youth, must have adequate calories for growth and development
Medical Therapy of Hyperlipidemia in Childhood

• 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors or statins
  – No large or long term studies
  – No proof of improvement in long term outcome
  – They are teratogenic! Girls must use contraception or abstinence
  – None-the-less, in small studies,
    • Lovastatin tolerated and effective
    • Pravastatin similar
Summary for Clinical Management of Safety Issues

- Measure baseline AST, ALT before statin use
- Can continue statins if ALT/AST are <3X upper limits of normal if monitor closely
- D/C statin if muscle symptoms appear and measure CPK
- If CPK is WNL or <3X normal, can continue statin and monitor symptoms. Consider dose reduction
- Statin must be discontinued if CPK is >10X normal

<table>
<thead>
<tr>
<th>Complication/Co-Morbid Condition</th>
<th>Indications and Intervals for Screening</th>
<th>Screening Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyslipidemia</td>
<td>Screening should commence at diagnosis of diabetes and every 1–3 years thereafter, as clinically indicated</td>
<td>Fasting TC, HDL-C, triglycerides, and calculated LDL-C</td>
</tr>
<tr>
<td>Hypertension</td>
<td>At diagnosis of diabetes and at every diabetes-related clinical encounter thereafter (at least twice annually)</td>
<td>BP measurement using appropriate-sized cuff</td>
</tr>
<tr>
<td>NAFLD</td>
<td>Yearly screening commencing at diagnosis of diabetes</td>
<td>ALT</td>
</tr>
<tr>
<td>Nephropathy</td>
<td>Yearly screening commencing at diagnosis of diabetes</td>
<td>• First morning (preferred) or random ACR.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Abnormal ACR requires confirmation at least 1 month later with a first morning ACR, and if abnormal, follow-up with timed, overnight or 24-hour split urine collections for albumin excretion rate.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Repeated sampling should be done every 3–4 months over a 6- to 12-month period to demonstrate persistence.</td>
</tr>
<tr>
<td>Neuropathy</td>
<td>Yearly screening commencing at diagnosis of diabetes</td>
<td>Questioned and examined for:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Symptoms of numbness, pain, cramps, and paresthesia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Skin sensation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Vibration sense</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Light touch, and</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Ankle reflexes</td>
</tr>
<tr>
<td>PCOS</td>
<td>Yearly screening commencing at puberty in women with oligo-amenorrhea, acne and/or hirsutism</td>
<td>Androgen levels including DHEAS and free testosterone</td>
</tr>
<tr>
<td>Retinopathy</td>
<td>Yearly screening commencing at diagnosis of diabetes</td>
<td>• 7-standard field, stereoscopic-color fundus photography with interpretation by a trained reader (gold standard); or</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Direct ophthalmoscopy or indirect slit-lamp fundoscopy through dilated pupil; or</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Digital fundus photography</td>
</tr>
</tbody>
</table>

Where is the Lesion in Poor Control of Diabetes Mellitus?

- The biology is now relatively easy to manage
- Tight Control, however is more difficult
- Poor control of Diabetes Mellitus is a condition that resides between the ears more than in the pancreas
  - Compliance?
  - Quality of life?
  - Normal human inertia?
Conclusions

• Type 2 Diabetes occurs in an individual with a genetic background in which the environment brings out the tendency
• Screening is appropriate for select children for T2 DM and other insulin resistant conditions
• Treatment choice is based upon presentation
• Comorbidities must be sought out and treated