Insulin Resistance
Type 2 Diabetes and NASH

SANDRA G HASSINK, MD, FAAP
DIRECTOR NEMOURS OBESITY INITIATIVE
A I DUPONT HOSPITAL FOR CHILDREN
WILMINGTON DE
Increased risk of MGDM

Intrauterine environment

- Infants born to diabetic mothers
  - Increased adiposity in childhood
  - Increased risk of obesity, impaired glucose tolerance and type 2 diabetes.

- Exposure to excess of glucose resulting in hyperinsulinemia in utero may alter insulin receptor expression and insulin sensitivity to the extra uterine environment.

- Infants born small for gestational age
  - Increased incidence of obesity at ages 7-11.

- Intrauterine growth in a restrictive nutritional environment due to maternal under nutrition may lead to exposure to increased amounts of fatty acids which may stimulate adipose tissue hyperplasia and insulin resistance.
  - Dunger DB, Ong KK. Horm Res. 2005;64 Suppl 3:58-65. Epub 2006 Jan 20
Testing for T2DM in Asymptomatic Children

- Criteria Overweight (BMI >85th percentile for age and sex, weight for height >85th percentile, or weight >120% of ideal for height)
- Plus any two of the following risk factors:
  - 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, PCOS, or birth weight small for gestational age birthweight)
  - Maternal history of diabetes or GDM during the child's gestation
- Age of initiation: 10 years or at onset of puberty, if puberty occurs at a younger age
- Frequency: every 3 years

American Diabetes Association Standards of medical care in Diabetes Care 2012 Jan;35 Suppl 1:S11-63
Acanthosis Nigricans

- Hyperpigmentation and velvety thickening that occurs in neck, axilla, groin, can occur over knuckles
- Seen in malignancies and other insulin resistant syndromes.
- Obese pediatric pts with acanthosis have higher fasting insulin and lower insulin sensitivity than acanthosis negative obese patients
- Insulin resistant pts were more likely to be obese (88%) than have acanthosis (65%)


https://online.epocrates.com/data_
Table 3—Categories of increased risk for diabetes (prediabetes)*

<table>
<thead>
<tr>
<th>Category</th>
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<tbody>
<tr>
<td>FPG 100 mg/dL (5.6 mmol/L) to 125 mg/dL (6.9 mmol/L) (IFG)</td>
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<tr>
<td>OR</td>
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<tr>
<td>2-h plasma glucose in the 75-g OGTT</td>
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<tr>
<td>140 mg/dL (7.8 mmol/L) to 199 mg/dL (11.0 mmol/L) (IGT)</td>
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<tr>
<td>OR</td>
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<tr>
<td>A1C 5.7–6.4%</td>
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*For all three tests, risk is continuous, extending below the lower limit of the range and becoming disproportionately greater at higher ends of the range.
Reproducibility of 2 hr OGTT in 60 Children

- 10 with IGT on first test
- 3 of these with IGT on 2\textsuperscript{nd} test
- % agreement with sequential OGTT was
  - IFG: 22.2%
  - IGT: 27.3%
- FBG more reproducible than 2 hour BG
- Discordant BG were more insulin resistant
  - Libman IM. Reproducibility of the Oral Glucose Tolerance Test in Overweight Children. JCEM, August 19, 2008 (on-line)
- FBG missed 70-90\% of youth with abnormal 2 hr BG (Arslanian)

Courtesy Dr. J Silverstein
Impaired fasting glucose/Impaired glucose tolerance (pre diabetes)

- Individuals with IFG and/or IGT have been referred to as having pre diabetes, indicating the relatively high risk for the future development of diabetes.
- IFG and IGT should not be viewed as clinical entities in their own right but rather risk factors for diabetes as well as cardiovascular disease (CVD).
- IFG and IGT are associated with obesity (especially abdominal or visceral obesity), dyslipidemia with high triglycerides and/or low HDL cholesterol, and hypertension.

Risk assessment

- As with glucose measurements, the continuum of risk is curvilinear, so that as A1C rises the risk of diabetes rises disproportionately

- Interventions should be most intensive and follow-up should be particularly vigilant for those with A1Cs >6.0%, who should be considered to be at very high risk.
Prevention of T2DM (Adults)

• Individuals at high risk for developing type 2 diabetes
  ○ Structured programs that emphasize lifestyle changes
    ▫ Moderate weight loss (7% body weight)
    ▫ Regular physical activity (150 min/week)
    ▫ Dietary strategies (reduced calories, reduced intake of dietary fat. (A)
    ▫ Dietary fiber (14 g fiber/1,000 kcal) and foods containing whole grains (one-half of grain intake). (B)
    ▫ limit their intake of sugar-sweetened beverages. (B)
  • The Diagnosis and Management of Non-Alcoholic Fatty Liver Disease: Practice Guideline by the American Association for the Study of Liver Diseases, American, Chalasani N, Younossi Z, Lavine J, Diehl A M, Brunt E MD, Cusi K, Charlton M, Sanyal A, College of Gastroenterology, and the American Gastroenterological Association HEPATOLOGY, Vol. 55, No. 6, 20122005-2021
Prevention/Delay of T2DM (Adults)

- Follow-up counseling appears to be important for success. (B)
- Based on the cost-effectiveness of diabetes prevention, such programs should be covered by third-party payers. (B)
- Metformin therapy for prevention of type 2 diabetes may be considered in those with IGT (A), IFG (E), or an A1C of 5.7–6.4% (E), especially for those with BMI >35 kg/m², age <60 years, and women with prior GDM. (A)
- At least annual monitoring for the development of diabetes in those with prediabetes is suggested. (E)

Lifestyle Interventions

- RCTs have shown that individuals at high risk for developing type 2 diabetes (those with IFG, IGT, or both) can significantly decrease the rate of onset of diabetes
  - Follow-up of three large studies of lifestyle intervention has shown sustained reduction in the rate of conversion to type 2 diabetes, with 43% reduction at 20 years in the Da Qing study
  - 3% reduction at 7 years in the Finnish Diabetes Prevention Study (DPS) and 34% reduction at 10 years in the U.S. Diabetes Prevention Program Outcome Study (DPPOS)
  - A cost-effectiveness model suggested that lifestyle interventions as delivered in the DPP are cost-effective
Prediction of Progression

- Strong, continuous association between A1C and subsequent diabetes
- Those with an A1C between 5.5 and 6.0% had a substantially increased risk of diabetes with 5-year incidences ranging from 9–25%.
- An A1C range of 6.0 to 6.5% had a 5-year risk of developing diabetes between 25 to 50% and relative risk 20 times higher compared with an A1C of 5.0%
- In a community-based study of black and white adults without diabetes, baseline A1C was a stronger predictor of subsequent diabetes and cardiovascular events than fasting glucose
- Other analyses suggest that an A1C of 5.7% is associated with diabetes risk similar to that of the high-risk participants in the Diabetes Prevention Program (DPP).
Progression from Pre-Diabetes to Diabetes in Adolescents

117 obese children and adolescents

At T=0: 33 (28%) had IGT
At 2 years:
- 8 IGT subjects developed T2D (24.2%)
- 15 IGT subjects reverted to NGT (45.5%)
- 10 IGT subjects remained IGT (30.3%)

Best predictors of development of T2D:
- Severe obesity (BMI ≥ 97th percentile) and persistent weight gain
- Relative with T2DM
- Increased insulin resistance (puberty, ethnicity, inactivity, visceral fat distribution, PCOS)


American Diabetes Association *Diabetes Care* 2000;23(3) 381-389.

Courtesy Dr. J Silverstein
Prevention of Diabetes in Adolescents

- Studies in adolescents have demonstrated increase in insulin sensitivity with diet and exercise induced weight loss

- Multicomponent lifestyle program showing in addition resolution of impaired glucose tolerance
  - Savoye M, Shaw M, Dziura et al 2007 Effects of a weight management program on body composition and metabolic parameters in overweight children; a randomized controlled trial. JAMA 297;2698-2704.
Exercise

- Improves insulin resistance in obese children when exercise capacity improved without changes in body weight or body composition.
- The specific exercise intervention changes from study to study. Exercise interventions ranged from 3-1 hour circuit training sessions/week, to 3,20-45 min sessions/week using sports activities, to progressive resistance training.
- Individual differences in physiologic changes with exercise
- Baseline fitness is dependent on genetic effects as well as lifestyle factors.
- Structured exercise remains a mainstay of therapeutic intervention in diabetes prevention.
Diagnosis of Diabetes

A1C ≥6.5%. 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 WHO, using a glucose load containing the equivalent of 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)

*In the absence of unequivocal hyperglycemia, result should be confirmed by repeat testing.
## Incidence of Type 2 Diabetes

<table>
<thead>
<tr>
<th>Ethnicity</th>
<th>10-14 yrs</th>
<th>15-19 yrs</th>
</tr>
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<tbody>
<tr>
<td>Native American</td>
<td>25.3/100,000person yrs</td>
<td>49.4</td>
</tr>
<tr>
<td>African American</td>
<td>22.3</td>
<td>19.4</td>
</tr>
<tr>
<td>Asian/Pacific Islander</td>
<td>11.8</td>
<td>22.7</td>
</tr>
<tr>
<td>Hispanic</td>
<td>8.9</td>
<td>17.0</td>
</tr>
<tr>
<td>Non Hispanic White</td>
<td>3.0</td>
<td>5.6</td>
</tr>
</tbody>
</table>

*Dabelea D. et al. "JAMA 2007;297:2716-2724*
Hemoglobin A1C

- 2009 use of HgbA1C test to diagnose diabetes recommended with a threshold of ≥6.5%
- ADA adopted this criterion in 2010
  - The diagnostic test should be performed using a method that is certified by the National Glycohemoglobin Standardization Program (NGSP) and standardized or traceable to the Diabetes Control and Complications Trial (DCCT) reference assay.
  - Point-of-care A1C assays, for which proficiency testing is not mandated, are not sufficiently accurate at this time to use for diagnostic purposes
Hemoglobin A₁C

- A₁C cut point of ≥6.5% identifies one-third fewer cases of undiagnosed diabetes than a fasting glucose cut point of ≥126 mg/dL (7.0 mmol/L)
  - Thus, the lower sensitivity of A₁C at the designated cut point may well be offset by the test's greater practicality, and wider application of a more convenient test (A₁C) may actually increase the number of diagnoses made.
  - American Diabetes Association Standards of medical care in Diabetes Care 2012 Jan;35 Suppl 1:S11-63
Hemoglobin A1C

- Epidemiologic datasets show a similar relationship between A1C and risk of retinopathy as FPG and 2-h PG thresholds.
- The A1C has several advantages to the FPG and OGTT
  - Greater convenience (since fasting is not required)
  - Greater preanalytical stability
  - Less day-to-day perturbations during periods of stress and illness.
- Disadvantages
  - Greater cost (glucose $5-40, HgbA1C $40-60)
  - Limited availability of A1C testing in certain regions of the developing world
  - Incomplete correlation between A1C and average glucose in certain individuals.
Hemoglobin A1C Population Differences

- **HbA1c levels may vary with patients’ race/ethnicity**

- **Matched for FPG, African Americans (with and without diabetes) had higher A1C than whites**
  - Glycemic burden (particularly postprandially) may be higher

- **No epidemiologic studies in children**
Abnormal hemoglobin but normal red cell turnover, such as sickle cell trait, an A1C assay without interference from abnormal hemoglobin should be used.

For conditions with abnormal red cell turnover, such as pregnancy, recent blood loss or transfusion, or some anemias, the diagnosis of diabetes must employ glucose criteria exclusively.

Confirming the Diagnosis

- Positive diagnostic test, repeat to rule out laboratory error, unless the diagnosis is clear on clinical grounds, hyperglycemic crisis or classic symptoms of hyperglycemia and a random plasma glucose ≥200 mg/dL.

- Repeat the same test for confirmation, e.g. if the A1C is 7.0% and a repeat result is 6.8%, the diagnosis of diabetes is confirmed.
  - However, if two different tests (such as A1C and FPG) are both above the diagnostic thresholds, the diagnosis of diabetes is also confirmed.

- If two different tests are available with discordant results, the test whose result is above the diagnostic cut point should be repeated, and the diagnosis is made on the basis of the confirmed test.
Therapy for Type 2 Diabetes

• At the time of type 2 diabetes diagnosis, initiate metformin therapy along with lifestyle interventions, unless metformin is contraindicated. (A)

• In newly diagnosed type 2 diabetic patients with markedly symptomatic and/or elevated blood glucose levels or A1C, consider insulin therapy, with or without additional agents, from the outset. (E)

• If noninsulin monotherapy at maximal tolerated dose does not achieve or maintain the A1C target over 3–6 months, add a second oral agent, a GLP-1 receptor agonist, or insulin. (E)
Medical Nutrition Therapy

- Clinical trials/outcome studies of MNT have reported decreases in A1C at 3–6 months ranging from 0.25 to 2.9% with higher reductions seen in type 2 diabetes of shorter duration.

- Multiple studies have demonstrated sustained improvements in A1C at 12 months and longer when an registered dietitian provided follow-up visits ranging from monthly to three sessions per year.
Weight Loss and Diabetes

- Look AHEAD (Action for Health in Diabetes) is a large clinical trial designed to determine whether long-term weight loss will improve glycemia and prevent cardiovascular events in subjects with type 2 diabetes.
  - One-year results of the intensive lifestyle intervention in this trial show an average 8.6% weight loss, significant reduction of A1C, and reduction in several CVD risk factors with benefits sustained at 4 years
Exercise

- Exercise is an important part of the diabetes management plan. Regular exercise has been shown to improve blood glucose control, reduce cardiovascular risk factors, contribute to weight loss, and improve well-being.
- Structured exercise interventions of at least 8-week duration have been shown to lower A1C by an average of 0.66% in people with type 2 diabetes, even with no significant change in BMI
- Higher levels of exercise intensity are associated with greater improvements in A1C and in fitness
Follow-up Treatment of Type 2 DM in Children & Adolescents

- diet/exercise + metformin
  - monthly review x 3 mo
  - failure
    - Add insulin or 2nd agent
    - failure
      - add a 2nd oral agent or insulin or incretins
  - success!!
    - continue
Goals of Treatment T2DM

- Physical well being, Psychological well being
- Weight loss or no further weight gain/Continued normal linear growth
- Long term glycemic control
- Control hypertension and hyperlipidemia
  - Hassink SG, Pediatric Weight Mgmt and Obesity, 2007 Lippincott Phila, Pa
- Family involvement
- Education including a basic knowledge of pathophysiology and short and long term complication
- Nutrition and meal planning
- Exercise
- Pharmacologic management
- Self monitoring.
- Ongoing monitoring of glucose, HgbA1C, Bun/Crt, LFT’s, microalbuminuria, lipids, dilated eye examination, neurologic and foot
Therapy for Type 2 Diabetes

- Weight loss is recommended for all overweight or obese individuals who have or are at risk for diabetes. (A)
- For weight loss, either low-carbohydrate, low-fat calorie-restricted, or Mediterranean diets may be effective in the short-term (up to 2 years). (A)
- For patients on low-carbohydrate diets, monitor lipid profiles, renal function, and protein intake (in those with nephropathy), and adjust hypoglycemic therapy as needed. (E)
- Physical activity and behavior modification are important components of weight loss programs and are most helpful in maintenance of weight loss. (B)

Pharmacologic Management - Metformin

- In patients with both IFG and IGT + 1 of the following:
  - <60 yo
  - BMI >35 kg.m²
  - FH DM in first degree relatives
  - High TG
  - Low HDL-C
  - HTN
  - A1c >6%
- Metformin approved in children >10 years
  - Decreases hepatic gluconeogenesis, increases insulin sensitivity, and lower triglycerides and LDL cholesterol
  - Nausea, vomiting, fullness, constipation, heartburn
  - Lactic acidosis

Pharmacologic Management- Insulin

- If metformin contraindicated
  - Renal insufficiency, Liver disease
  - Alcohol abuse,
  - Hypoxemia
  - Hypoperfusion
  - Sepsis
  - Discontinue with contrast dye, serious illness
  - Vitamin B12 deficiency reported in adults with long term use.
- If metabolic control cannot be achieved with lifestyle and metformin
- If beta cell failure (in adults 6-8 yrs after diagnosis)
Bariatric surgery may be considered for adults with BMI >35 kg/m² and type 2 diabetes, especially if the diabetes or associated comorbidities are difficult to control with lifestyle and pharmacologic therapy.

Insulin Resistance

Type 2DM
NASH
PCOS
Dyslipidemia
Hypertension
Polycystic Ovarian Syndrome

- Polycystic Ovary Syndrome.
  - Hyperandrogenism
  - Oligomenorrhea/amenorrhea.
  - Hirsuitism
  - Acne
  - Polycystic ovaries and eventual infertility.

- Increased risk
  - Girls with premature adrenarche
    - Bacha F, Arslanian S. Enod Trends 11(1)2004
Non Alcoholic Steatohepatitis - Obesity

- **Diagnosis**
  - Increased liver enzymes and fatty liver on ultrasound in the absence of other causes of liver disease.
  - Rule out other causes of fatty liver
  - Liver Biopsy

- **Etiology**
  - 20%-25% obese children have evidence of steatohepatitis.
  - Obesity and type 2 diabetes are the strongest predictors of progression of fibrosis
  - Age is also a risk factor for cirrhosis which may reflect increased duration of risk for the “second hit” thought to initiate fibrosis.

- **Penetrance of NAFLD**
  - Family members of children with NAFLD.
NASH risk

- Predictors of elevated serum ALT in obese children
  - Male gender
  - Hispanic ethnicity
  - Elevated BMI
  - Insulin resistance (HBP, metabolic syndrome, dyslipidemia)

- Predictors of fibrosis
  - Obesity (BMI z score)
  - Insulin resistance
  - Leptin (?)
    - Schwimmer, J B et al Pediatr 2003 143(4), 500-505

- “A liver NAFLD runs a higher risk of being damaged by other factors, from viruses to endotoxins, from alcohol to industrial toxic compounds”
  - Yang SO, Lin HZ, Lane MD, Clemens M, Diehl AM. Proc Natl Acd Sci USA 1997; 94: 25572562
NAFLD Prevalence

- A school-based study of obese children ALT >40U/L
  - 23% of 17-18 year olds elevated unexplained ALT.

- Autopsy study using the “gold standard” of liver histology
  - estimated NAFLD prevalence was 9.6%

- Multivariate analyses showed that obesity, older age (in adolescence), male gender, and Hispanic ethnicity independent predictors of fatty liver prevalence.
Pronounced features of hepatocellular injury, lobular inflammation, and peri-sinusoidal fibrosis,

Unique pattern of unclear significance marked macrovesicular hepatocellular steatosis, portal inflammation and portal fibrosis in the absence of ballooning.

NAFLD to NASH

- Genetic Predisposition
- Obesity
- Fatty Liver/Steatosis
  - 2nd “Hit”
- Inflammation
- Fibrosis
- Cirrhosis

Potential role of adipocyte dysfunction and nontraditional risk factors in the development of NAFLD and its relationship with CMD.

Adipocyte dysfunction
- IL-6 ↑
- TNF-α ↑
- Leptin ↑
- RBP4 ↑
- Adiponectin ↓
- Resistin ↑

Mitochondrial dysfunction
↑IL-6, ↑TNF-α

Oxidative stress

High FFA flux
Hyperglycemia
Hyperinsulinemia

The Spectrum of NAFLD
- Fatty Liver
- NASH
- Cirrhosis

Genes
Lifestyle

Energy imbalance

Fat accumulation

Adipose tissue

Inflammation
- CRP ↑
- Fibrinogen ↑

Cellular Insulin Resistance

CMD

FFA: Free Fatty Acids
CRP: C-Reactive Protein
IL-6, TNF-α: Inflammatory cytokines
Leptin, RBP4, Adiponectin: Adipokines
Resistin: Adipokine
Hyperglycemia, Hyperinsulinemia: Metabolic aberrations
FFA flux: Lipotoxic stress
Oxidative stress: Mitochondrial dysfunction
Cirrhosis: Advanced stage of liver damage
NASH: Non-alcoholic steatohepatitis
Fatty Liver: Mild stage of liver damage
High FFA flux, Hyperglycemia, Hyperinsulinemia: Metabolic syndrome
Adipocyte dysfunction, Inflammation: Cascade of events leading to NAFLD and CMD
Treatment NAFLD

• Recommendations
  ○ Include consultation with a registered dietitian to assess quality of diet and measurement of caloric intake, adoption of American Heart Association dietary strategies, and regular aerobic exercise progressing in difficulty as fitness allows.
  
  • BARLOW SE, DIETZ WH. MANAGEMENT OF CHILD AND ADOLESCENT OBESITY: SUMMARY AND RECOMMENDATIONS BASED ON REPORTS FROM PEDIATRICIANS, PEDIATRIC NURSE PRACTITIONERS, AND REGISTERED DIETITIANS. PEDIATRICS 2002;110:236-238.
NASH - Treatment

- Loss of at least 10% of their excess weight normalized ALT and AST values and decreased ultrasound evidence of fatty infiltration

- Clinical trial (TONIC)
  - Compared the efficacy of vitamin E or metformin to placebo in 8-17 year olds with NAFLD.
  - Primary outcome of sustained reduction of ALT was not different among the 3 groups
  - Statistically significant improvements in NAS and resolution of NASH (P<0.006) with vitamin E treatment compared to placebo over 96 weeks.
    - Confirmatory studies needed

- Metformin administered at 500 mg twice daily dose had no effect on liver biochemistries or liver histology