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Diagnostic Criteria and Measurements for Detection of Insulin Resistance and Type 2 Diabetes

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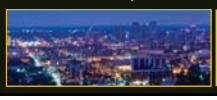



Objectives

1. Prevalence of and pathogenesis of type 2 diabetes
2. Review current American Diabetes Association criteria for diagnosis of insulin resistance and type 2 diabetes
3. Examine traditional clinical measurements used to diagnose and manage type 2 diabetes
4. Discuss current and emerging tools for detection of insulin resistance/type 2 diabetes

Diabetes Facts

Prevalence in the United States

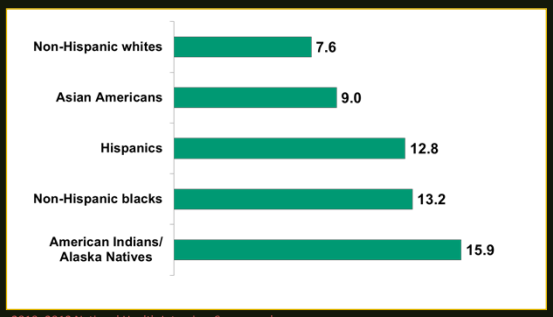
- Diagnosed cases of diabetes increased by 128% from 1988 to 2008
- 25.8 million Americans (8.3%) have diabetes
- > 85% of people with type 2 diabetes are overweight or obese

Complications of Diabetes

- Heart disease noted on 68% of diabetes-related death certificates (2-4 fold increase in risk)
- Leading cause of blindness and kidney failure
- 60-70% have mild to severe neuropathy
- 65,700 amputations are performed annually

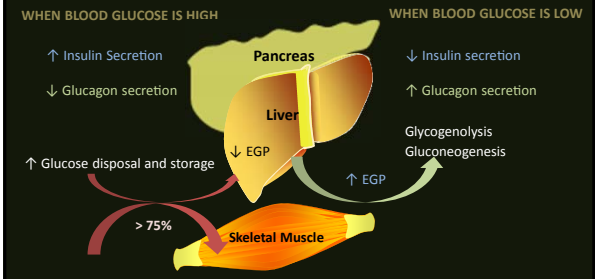
http://professional.diabetes.org

Prevalence of Diabetes



2010–2012 National Health Interview Survey and
2012 Indian Health Service's National Patient Information Reporting System

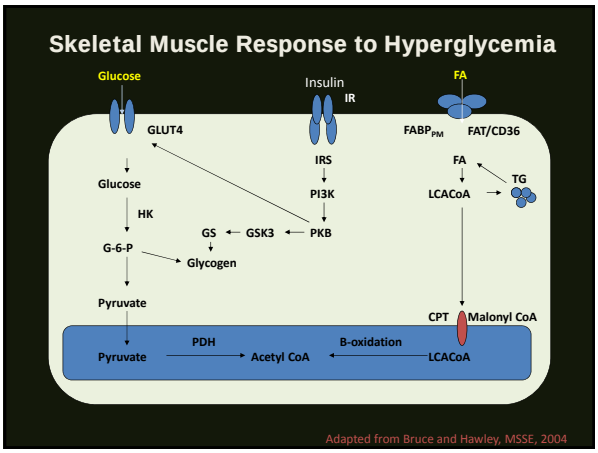
Metabolic Responses to Blood Glucose

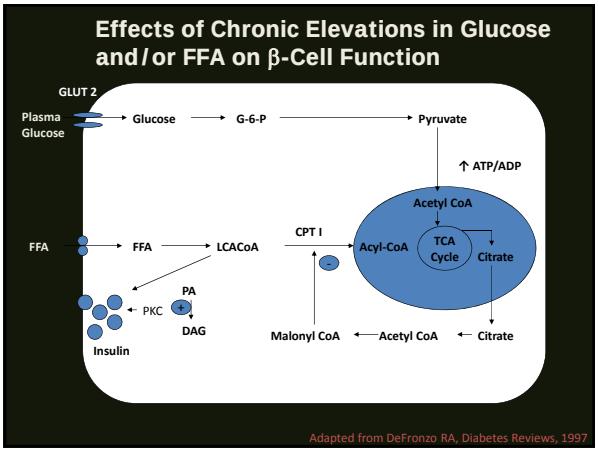


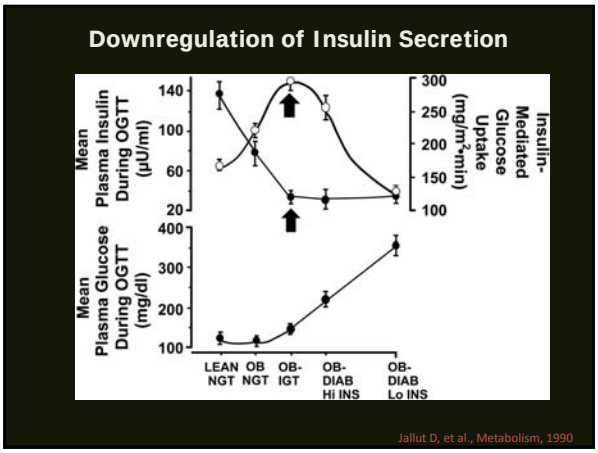
Adapted from: Defronzo RA, Diabetes Reviews, 1997

Pancreatic Response to Hyperglycemia

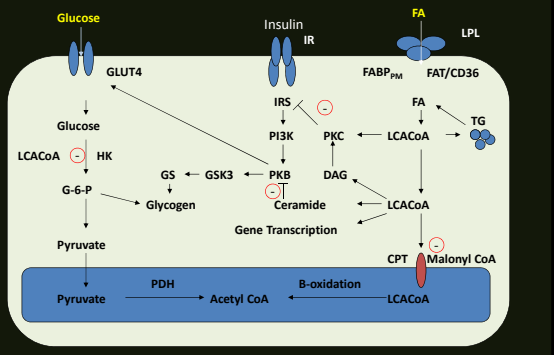
http://wp-content/uploads/2011/03/insulin-secretion-w500.jpg


Skeletal Muscle Response to Hyperglycemia
Glucose
Insulin
IR
FA
GLUT4
FABP$_{PM}$
FAT/CD36
IRS
FA
TG
Glucose
PI3K
LCACoA
HK
GS
GSK3
PKB
G-6-P
Glycogen
Pyruvate
CPT
Malonyl CoA
PDH
B-oxidation
Pyruvate
Acetyl CoA
LCACoA
Adapted from Bruce and Hawley, MSSE, 2004


Effects of Chronic Elevations in Glucose and/or FFA on β-Cell Function
GLUT 2
Plasma Glucose
Glucose
G-6-P
Pyruvate
ATP/ADP
Acetyl CoA
FFA
FFA
LCACoA
CPT I
Acyl-CoA
TCA Cycle
Citrate
PA
PKC
DAG
Insulin
Malonyl CoA
Acetyl CoA
Citrate
Adapted from DeFronzo RA, Diabetes Reviews, 1997


Downregulation of Insulin Secretion
Mean Plasma Insulin During OGTT (μU/ml)
140
100
60
20
Insulin-Mediated Glucose Uptake (mg/m^2•min)
300
250
200
150
100
Mean Plasma Glucose During OGTT (mg/dl)
400
300
200
100
LEAN NGT
OB NGT
OB-IGT
OB-DIAB Hi INS
OB-DIAB Lo INS
Jallut D, et al., Metabolism, 1990

Skeletal Muscle Insulin Resistance



Adapted from Bruce and Hawley, MSSE, 2004

Clinical Criteria for Diagnosis of Pre-Diabetes and Diabetes

Pre-diabetes

- Impaired Fasting Glucose (IFG) 100 -125 mg/dL
- Impaired Glucose Tolerance (IGT) 140-149 mg/dL

Diabetes

- Fasting plasma glucose ≥ 126 mg/dL
- Oral glucose tolerance test ≥ 200 mg/dL
- Hemoglobin A1C (HbA1c) ≥ 6.5%
- Random plasma glucose ≥ 200 mg/dL

Clinical Criteria for Diagnosis of Diabetes

Fasting Plasma Glucose (FPG)

- Fasting is defined as no caloric intake for at least 8 hours
- Should be repeated once

Oral Glucose Tolerance Test

- Use a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water
- Measure blood glucose response 2 hours later
- Should be repeated once

Clinical Criteria for Diagnosis of Diabetes

HbA1c

- Correlates well with microvascular disease
- Advantages
  - Fasting is not required
  - Lower day to day perturbations
- Disadvantages
  - Cost
  - Can be misleading in patients with anemia from hemolysis or iron deficiency
  - Identifies 1/3 fewer cases of undiagnosed diabetes than fasting blood glucose ≥ 126
- Should be repeated once to confirm. If criterion for A1C (≥ 6.5%) is met but not the FPG (i.e. < 126 mg/dL), diagnosis of type 2 diabetes should be made

Clinical Criteria for Diagnosis of Diabetes

Random Plasma Glucose

- ≥ 200 mg/dL
- Classic symptoms of hyperglycemia or hyperglycemic crisis

Direct Measurement of Insulin Sensitivity

Hyperinsulinemic-Euglycemic Clamp

Antecubital vein infusion catheter and contralateral dorsal vein sampling catheter

↓

Constant insulin infusion (hyperinsulinemia) (5 – 120 mU/m^2/min)

↓

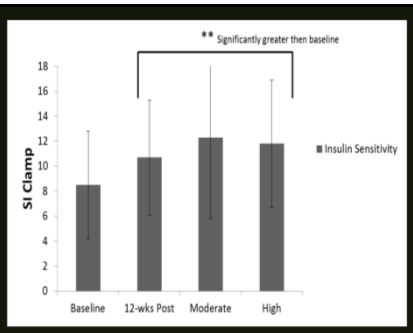
20% dextrose infused to maintain euglycemia (e.g. 100 mg/dL) by measuring PG every 5-10 minutes

↓

Greater glucose infusion rate = greater insulin sensitivity

*Assumes that hyperinsulinemia suppresses HGP. Since no net change occurs in PG under the "clamp", GIR must be equal to disposal rate (M). Tracers (3-^{3}H glucose) and/or ↑ insulin infusion

DeFronzo RA, et al., Am J Physiol Endocrinol Metab Gastrointest Physiol, 1979



Fisher G, et al., Unpublished

$SI_{Clamp} = M / (G \times \Delta I)$

Where M = GIR/[SSPG] and ΔI = Difference between fasting and SSPI

Katz A, et al. J Clin Endocrinol Metab, 2000

Insulin Suppression Test (IST)

Overnight Fast

Somatostatin (250 µg/h) to suppress endogenous secretion of insulin and glucagon. Insulin (25 mU/m^2/min and glucose (240 mg/m^2/min) are infused in an antecubital vein for 3h

Minute	0	30	60	90	120	150	160	170	180

Blood Sampling

Constant infusion of insulin and glucose will determine steady-state plasma insulin (SSPI) and glucose (SSPG) concentrations

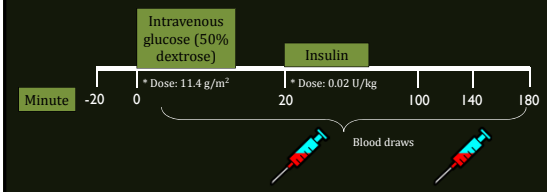
SSPI is similar between participants. SSPG is higher in insulin-resistant than insulin sensitive participants

Provides a direct measure (SSPG) of exogenous insulin to mediate disposal of an IV glucose load under SS where exogenous insulin secretion is suppressed

Shen S, et al., J Clin Invest, 1970; Harano Y et al, Metabolism, 1978

Indirect Measurement of Insulin Sensitivity

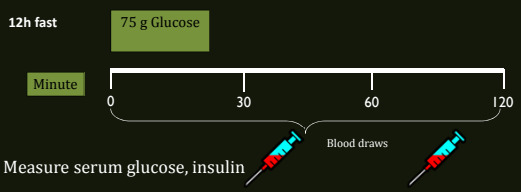
Intravenous Glucose Tolerance Test



Measure serum glucose, insulin

Insulin sensitivity (S_I) calculated using the "MINMOD" computer program (ver. 3, Bergman)

Oral Glucose Tolerance Test



Measure serum glucose, insulin

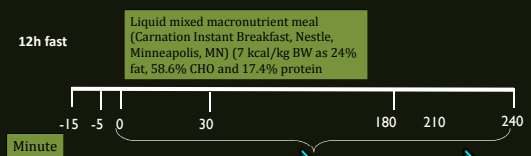
Reflects the efficiency of the body to dispose of glucose after an oral glucose load

Mimics glucose and insulin dynamics more closely than the clamp. However, insulin, incretins and other factors contribute to GT (GT not equal to IS)

Meal Tolerance Test

12h fast

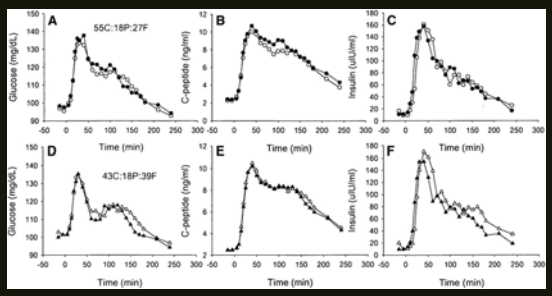
Liquid mixed macronutrient meal (Carnation Instant Breakfast, Nestle, Minneapolis, MN) (7 kcal/kg BW as 24% fat, 58.6% CHO and 17.4% protein



Measure serum glucose, insulin

Blood sampling every 5 minutes from time 0 to 30 min
Blood sampling every 10 minutes from time 30 to 180 min
Mimics glucose and insulin dynamics more closely than the clamp.
However, insulin, incretins and other factors contribute to GT

Goree L, et al., Am J Clin Nutr, 2011



Goree L, et al., Am J Clin Nutr, 2011

Surrogates Derived from Fasting Steady-State Conditions

1/Fasting Insulin

- Elevations in fasting insulin levels (with normal fasting glucose levels) correspond to increased insulin resistance
- Decreases as fasting insulin rises with insulin resistance
- Does not take into account low insulin secretion in the face of hyperglycemia seen in diabetes or glucose intolerance

Homeostasis Model Assessment

- Used to predict fasting SSPG and insulin concentrations
- Assumes a feedback loop exists between liver and β-cells where glucose concentrations are regulated by insulin-dependent HGP (Insulin levels depend on the pancreatic response to glucose)

HOMA-IR = {[fasting insulin (μU/mL)] x [fasting glucose (mmol/L)]/22.5

- 22.5 is a normalizing factor derived from "normal" fasting insulin (5 μU/mL) and FPG (4.5 mmol/L)
- "Normal" insulin sensitivity, HOMA-IR = 1

Matthews DR, et al., Diabetologia, 1985

Homeostasis Model Assessment

- HOMA-IR correlates with glucose clamp (Fisher G et al., unpublished)
- Over wide ranges of insulin sensitivity (IFG), transformation of fasting insulin values improves relationship with glucose clamp
- HOMA-IR did not correlate with glucose clamp following an exercise intervention where insulin sensitivity improved via glucose clamp. Suggests that improvements in insulin sensitivity with exercise are in skeletal muscle (HOMA-IR is a better reflection of liver insulin sensitivity) (Fisher G et al., unpublished)
- Does not correlate with glucose clamp in individuals with β-cell dysfunction

Matthews DR, et al., Diabetologia, 1985

Quantitative Insulin Sensitivity Check Index (QUICKI)

QUICKI = 1/[log (fasting insulin, μU/mL) + log (fasting glucose, mg/dL)]

- QUICKI is more strongly correlated with SI_{Clamp} than SI from HOMA-IR
- Log HOMA-IR and QUICKI are comparable
- QUICKI is the most thoroughly evaluated and validated surrogate index for SI
- Changes in QUICKI with therapeutic interventions are significantly correlated with changes in SI clamp
  (Chen H, et al, Am J Physiol Endocrinol Metab, 2003; Katsuki A., et al. J Clin Endocrinol Metab 2002)

Katz A, et al., J Clin Endocrinol, 2000

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