Functional Medicine University's Functional Diagnostic Medicine Training Program

Mod 4 * FDMT533B

Primary and Advanced Testing: Assessing Blood Glucose Regulation

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New on-line library document available on FMU: *Procedures/Diagnostic Tests-Oral Glucose Tolerance Test* Patient Education Handout: Clinical Center National Institutes of Health

Required reading: *The Oral Glucose Tolerance Test Revisited*. This article may be found with the Insider's Guide and Handouts for this lesson and in the on-line library at www.FunctionalMedicineUniversity.com

The Four Types of Diabetes

1. Type 1 Diabetes
   - 5 to 10 percent of all diagnosed cases of diabetes. Risk factors include autoimmune, genetic, environmental, and viral.

2. Type 2 Diabetes
   - 90 to 95 percent of all diagnosed cases of diabetes. Risk factors include aging, obesity, family history, sedentary lifestyle, race/ethnicity, history of gestational diabetes, and impaired glucose tolerance.

3. Gestational diabetes
   - develops in 2 to 5 percent of all pregnancies. Resolves when pregnancy is over.

4. "Other Special Types"
   - results from specific genetic syndromes, surgery, drugs, malnutrition, infections, mDNA mutations, oxidative stress and other illnesses. Accounts for 1 to 2 percent of all diagnosed cases of diabetes. *Certain viruses have been associated with beta-cell destruction. Diabetes can occur in patients with congenital rubella, although most of these patients have HLA and immune markers characteristic of type 1 diabetes. In addition, coxsackievirus B, cytomegalovirus, adenovirus and mumps have been implicated in inducing certain cases of the disease.*[10]

Insulin resistance has been loosely defined as the requirement of 200 or more units of insulin per day to attain glycemic control and to prevent ketosis. Criteria from the National Cholesterol Education Program/Adult Treatment Panel III (NCEP/ATP III) are used to clinically identify patients with insulin resistance. The diagnosis of insulin resistance (metabolic syndrome) is established when three or more of the following are present:

- Abdominal Obesity-waist circumference more than 40 inches (102 cm) in men or more than 35 inches (88 cm) in women
- Fasting triglyceride level of 150 mg/dL or greater
- Blood pressure of 130/85 or greater
- HDL-C less than 40 mg/dL in men and less than 50 mg/dL in women
- Fasting glucose level of 100 mg/dL or higher

(Note: Detection, Evaluation, and High Blood Cholesterol in Adults (Adult Treatment Panel IV) expected release date is fall of 2011.)

Impaired Glucose Tolerance/Impaired Fasting Glucose

Impaired glucose tolerance and impaired fasting glucose form an intermediate stage in the natural history of diabetes mellitus. From 10 to 15 percent of adults in the United States have one of these conditions. Impaired glucose tolerance is defined as two-hour glucose levels of 140 to 199 mg/dL (7.8 to 11.0 mmol) on the 75 gram oral glucose tolerance test, and impaired fasting glucose is defined as glucose levels of 100 to 125 mg/dL (5.6 to 6.9 mmol/L) in fasting patients. These glucose levels are above normal but below the level that is diagnostic in fasting patients. Patients with impaired glucose tolerance or impaired fasting glucose have a significant risk of developing diabetes and are thus a target group for primary intervention. Risk factor for diabetes include family history of diabetes, body mass index greater than 25 kg/m^2, sedentary lifestyle, hypertension, dyslipidemia, history of gestational diabetes or large-for gestational-age-infant, and polycystic ovary syndrome.[1] The Atherosclerosis Risk in Communities Study concluded that two-thirds of subjects classified at the lower end of impaired fasting glucose (100-109mg/dL) had either diabetes or impaired glucose tolerance.[7] These studies appear to support the need for utilizing the functional medicine optimal range for serum glucose as the cut point.

Drug-induced Disorders of Glucose Tolerance

An investigative article written in the Annals of Internal Medicine concluded that many common therapeutic agents influence glucose metabolism and may cause hyperglycemia, hypoglycemia or both based on the circumstances at the time of use.[8] It was recommend that patients avoid such medication or, when not possible, to closely monitor plasma glucose.

Medications associated with *hyperglycemia* include, but not limited to:

- Thiazide diuretics
- Central acting alpha-blockers
- Beta-blockers
- Calcium-channel blockers
- Minoxidil
- Diazoxide
- Corticosteroids
- Cyclosporine
- Phenytion
- Oral contraceptives and sex hormones
- Nicotinic acid and niacin
- Phenothiazines
- Lithium
- Thyroid hormone
- Beta-adrenergic agonists

Medications associated with *hypoglycemia* include but not limited to:

- Salicylates and acetaminophen
- Sulfamethoxazole
- Beta-blockers
- Quinine
- Pentamidine
- Beta-2 agonists
- Disopyramide
- Ethanol
- Monoamine oxidase inhibitors and tricyclic antidepressants
- Angiotensin-converting enzyme inhibitors
- Alpha-blockers
- Fibric acid derivatives (gemfibrozil may increase plasma glucose levels)
- Stretozotocin

Statins Cause Diabetes[17]

A recently published meta-analysis of 13 randomized controlled trials that included a total of 91, 140 participants found that treatment with a cholesterol-lowering statin drug significantly increased the risk of developing diabetes. This new finding adds to the long list of adverse effects of statin drugs, which include myopathy (7%-15%), rhabdomyolysis, hepatotoxicity, cognitive dysfunction, memory loss, gastrointestinal symptoms, headaches, and skin rashes.
The article went on the say that pushing the cholesterol level below its usual set point decreases the body's capacity to synthesis beneficial steroids, such as vitamin D and DHEA.(I have heard discussions on whether or not cholesterol lowering drugs affect steroid synthesis. At present it seems to depend on the type of statin prescribed) DHEA and vitamin D have been shown to increase insulin sensitivity. The article also addressed the cardioprotective effect of statins. Statins drugs are known to lower CRP, however the risk to benefit ratio was questioned. Dr. Gaby suggested alternatives to statins, which include dietary modifications and nutritional supplementation. He also recommending eating foods that have low-AGE (advanced glycated end products). The use of red yeast rice was suggested as an alternative to statin drugs. Red yeast rice contains statin-like compounds and has significantly less side effects than statin drugs, but there is still a long term risk of developing diabetes.

Progression to Type II Diabetes

The American Association of Clinical Endocrinologists clinical criteria for diagnosis of insulin resistance syndrome include the NCEP/ATP III criteria, as well as, a 2-hour oral glucose tolerance test (OGTT). Impaired glucose tolerance has been shown to be an independent marker of cardiovascular disease (endothelial disease), which better identifies individuals at risk for endothelial damage caused by hyperglycemia.[2, 3]

GENETIC AND AQUIRED CONDITIONS
(examples of acquired conditions: obesity, sedentary lifestyle, nutritional deficiencies, increased free fatty acids)
↓
INSULIN RESISTANCE
↓
HYPERINSULINEMIA (according to various authorities, optimal range of serum fasting insulin is <5 or <10 microunits/mL)
↓
COMPENSATED INSULIN RESISTANCE (normal glucose tolerance)
IMPAIRED OPTIMAL FASTING GLUCOSE (> 95 mg/dL)
↓
IMPAIRED GLUCOSE TOLERANCE (2-hour glucose levels 140-199mg/dL)
IMPAIRED FASTING GLUCOSE (≥ 100 mg/dL)
↓
PANCREATIC BETA CELL FAILURE
(Beta cell failure can be due to genetics, glucostoxicity, oxidative stress, mitochondrial dysfunction and disease, and increased free fatty acid levels)
↓
INCREASED HEPATIC GLUCOSE OUTPUT
↓
TYPE II DIABETES

(Note: An increase in plasma free fatty acids observed in obesity and type 2 diabetes also induces markers for endothelial activation, vascular inflammation and thrombosis.[4] Free fatty acids are released into the bloodstream as a result of lipolysis in the fat cells. Overweight and obese patients have large reservoirs of fat cells that can elevate plasma free fatty acid levels. A defect found in type 2 diabetes is the inability of insulin to suppress hepatic glucose production.[9])

In July 2004, NCEP coordinating committee issued an update to the ATP III guidelines on the detection, evaluation, and treatment of high blood cholesterol (LDL-C) in adults

Recommendations for Modifications to Footnote the ATP III Treatment Algorithm for LDL-C

- Therapeutic lifestyle changes (TLC) remain an essential modality in clinical management. TLC has the potential to reduce cardiovascular risk through several mechanisms beyond LDL lowering.

- In high-risk persons, the recommended LDL-C goal is <100 mg/dL.

  – An LDL-C goal of <70 mg/dL is a therapeutic option on the basis of available clinical trial evidence, especially for patients at very high risk.

  – If LDL-C is ≥100 mg/dL, an LDL-lowering drug is indicated simultaneously with lifestyle changes.

  – If baseline LDL-C is<100 mg/dL, institution of an LDL-lowering drug to achieve an LDL-C level <70 mg/dL is a therapeutic option on the basis of available clinical trial evidence.

  – If a high-risk person has high triglycerides or low HDL-C, consideration can be given to combining a fibrate or nicotinic acid with an LDL-lowering drug. When triglycerides are ≥200 mg/dL, non-HDL-C is a secondary target of therapy, with a goal 30 mg/dL higher than the identified LDL-C goal.

- For moderately high-risk persons (2+ risk factors and 10-year risk 10% to 20%), the recommended LDL-C goal is <130 mg/dL; an LDL-C goal <100mg/dL is a therapeutic option on the basis of available clinical trial evidence. When LDL-C level is 100 to 129 mg/dL, at baseline or on lifestyle therapy, initiation of an LDL-lowering drug to achieve an LDL-C level <100 mg/dL is a therapeutic option on the basis of available clinical trial evidence.

- Any person at high risk or moderately high risk who has lifestyle-related risk factors (e.g., obesity, physical inactivity, elevated triglyceride, low HDL-C, or metabolic syndrome) is a candidate for TLC to modify these risk factors regardless of LDL-C level.

- When LDL-lowering drug therapy is employed in high-risk or moderately high-risk persons; it is advised that intensity of therapy be sufficient to achieve at least a 30% to 40% reduction in LDL-C levels.

- For people in lower-risk categories, recent clinical trials do not modify the goals and cutpoints of therapy.

(Note: The purpose of reviewing the modifications to ATP III is to familiarize you with the allopathic standard of care. Knowing this information will enable you to make discerning clinical decisions based on your knowledge of functional medicine.)

Diagnostic Studies

The diagnosis of insulin resistance is based on clinical findings collaborated with diagnostic studies. No single test is used to diagnose insulin resistance.

Screening tests for pre-diabetes and diabetes:

- Individuals 45 or older, especially if BMI is equal to or greater than 25kg/m^2 (yearly)

- Individuals younger than 45 if BMI is ≥ 25kg/m^2 and have additional risk factors such as; sedentary lifestyle, first degree relatives with diabetes, high risk ethic background (American Indian, Hispanic, African-American, Asian-American), history of gestational diabetes, delivered a baby >9 lbs, hypertension, low HDL-C, high serum triglycerides, polycystic ovary syndrome, impaired fasting glucose, obesity, acanthosis nigricans, history of cardiovascular disease.

(Note: *Acanthosis nigricans* is a skin condition characterized by dark thickened velvety patched, especially in the folds of skin in the axilla, groin and back of the neck. This condition is seen in insulin resistance, diabetes mellitus, Cushing disease, pituitary tumors, and certain carcinomas. Treatment of the underlying cause will help to resolve this condition.)

- Fasting plasma glucose – optimal range 80-95 mg/dL
- Oral glucose tolerance test (OGTT) – Longitudinal epidemiological studies indicate that about 40% of subjects who develop type 2 diabetes have normal glucose tolerance at baseline, indicating that there is a population of normal glucose tolerance subjects who are at risk for future type 2 diabetes.[5]An editorial in the "European Heart Journal" stated that the OGTT remains the most valuable tool for early recognition of persons diabetes or who are at increased risk for diabetes and heart disease.[6] The article went on to stated that post-challenge glucose identifies many individuals with diabetes who would be missed by fasting glucose or glycosylated hemoglobin.

The standard OGGT measures serum glucose concentration 2 hours after a 75 gram glucose load. The American Diabetes Association diagnostic criteria are as follows:

- Normal glucose regulation – fasting glucose < 100mg/dL and 2-hour OGGT <140mg/dL
- Impaired fasting tolerance (IFT) – fasting glucose ≥100mg/dL but <110mg/dL
- Impaired glucose tolerance (IGT) – 2-hour OGTT ≥140mg/dL but <200mg/dL
- Diabetes mellitus – (1) fasting glucose≥126mg/dL and a casual (random) glucose ≥200mg/dL, (2) casual glucose ≥200mg/dL on 2 occasions, or (3) the classic symptoms plus a 2-hour OGTT ≥200mg/dL.
- Gestational diabetes mellitus – any degree of glucose intolerance during pregnancy.

Required reading: *The Oral Glucose Tolerance Test Revisited.*
(This article may be located on the Functional University website with this lesson or the on-line library)

- Hemoglobin A1c (glycated hemoglobin or HBA1c) – measures the average amount of glucose in the blood over the last two to three months. Glucose in the blood can bind to hemoglobin forming a glucose-hemoglobin molecule, which remains there for the life of the red blood cell. Hemoglobin A1c is produced daily and slowly cleared from the blood as older red blood cells die.
    - Non-diabetic – 4% to 6%
    - Pre-diabetic – 5.7% to 6.4%
    - Diabetic - ≥6.5%

HbA1c %	Serum Glucose mg/dL
4.0-4.9	68-94
5.0-5.9	97-123
6.0-6.9	125-151
7.0-7.9	154-180
8.0-8.9	183-209
9.0-9.9	212-237
10.0-10.9	240-266
11.0-11.9	269-295
12.0-12.9	298-324
13.0-13.9	326-352

OPTIMAL HbA1c %	OPTIMAL SERUM GLUCOSE mg/dL
4.4	80
4.5	82
4.6	85
4.7	88
4.8	91
4.9	94

    - False low readings – anemia, sickle cell, heavy bleeding
    - False increased readings – iron deficiency, recent blood transfusion

- Liver Function Tests – Liver dysfunction and disease (cirrhosis) is a cause of glucose intolerance. Therefore, it is important to obtain a baseline panel.
- Electrolytes, BUN, creatinine, and uric acid – hyperuricemia is common in insulin resistance and is considered a component of the metabolic syndrome. (Remember increased uric acid levels and oxidative stress.)
- CBC – used to rule out anemia and infections

- Homocysteine – Elevated levels of fasting plasma homocysteine are associated with hyperinsulinemia and may partially account for increased risk of CVD associated with insulin resistance.[11] Elevated levels are a risk factor for atherosclerosis, which predicts microvascular disease. A study performed in 2008 showed a correlation of plasma homocysteine with insulin resistance in polycystic ovary symdrome.[12]

  Reference Ranges: male < 11.4 umol/L; female <10.4 umol/L

- Lipid Profile – Poor glycemic control is often associated with dyslipidemia. Insulin resistance is characterized by increased levels of LDL (pattern B), high triglyceride level, and decreased HDL-C. (LDL Pattern A and LDL Pattern B refer to the size of the LDL particles. Pattern B is predominately small dense LDL cholesterol particles and are associated with low HDL and elevated triglycerides. Pattern B individuals have a tendency to develop high blood glucose and type 2 diabetes [VAP test])

- Serum Insulin and C-peptide – Insulin and C-peptide are produced by the beta-cells of the pancreas as the result of proteolytic cleavage of proinsulin. Serum insulin and serum glucose must be in balance with one another. Hyperinsulinemia is associated with insulin resistance and insulinoma. Both can result in hypoglycemia leading. Symptoms of hypoglycemia include: sweating, palpitations, hunger, confusion, blurred vision, dizziness, fainting and seizure.

DYSFUNCTION/DISEASE	**FASTING INSULIN LEVEL**	**FASTING GLUCOSE LEVEL**
None	normal	normal
Insulin resistance (obesity, drug induced)	greatly increased	normal to somewhat increased
Decreased production of insulin (diabetes, pancreatitis, cystic fibrosis, pancreatic cancer, hypopituitarism)	greatly decreased	greatly increased
Hypoglycemia due to excess insulin (insulinoma, Cushing disease, excess exogenous insulin)	normal to greatly increased	greatly decreased

Reference ranges for serum insulin are:

- Tanner stage I: 2.6-15.5 microunits/mL
- Tanner stage II and III: 8.3-22.0
- Tanner stage IV and V: 8.5-23.0
- Adult: 6-27
- Proposed optimal range:10-15

Serum C-peptide can be use to evaluate patients with insulin-secreting neoplasm and to test for endogenous insulin production. C-peptide levels will be increased in insulinoma and decrease with beta-cell destruction. C-peptide is also useful in evaluating residual beta-cell function in insulin dependent diabetes.

Reference ranges for C-peptide are:

- 0-9 years: 0-3.3 ng/mL
- 10-16 years: 0.4-3.3 ng/mL
- >16 years: 1.1-5.0 ng/mL

- Fructosamine – fructosamine is a measure of glycated protein. Fructosamine testing shows glucose levels over the past 2 to 3 weeks. Assessing fructosamine is useful in situations where HbA1c cannot be readily measured. High levels of vitamin C, lipemia, hemolysis and hyperthyroidism can interfere with test results. False low levels can result from a decrease in total protein and/or albumin levels.

Approximate Comparison of Blood Glucose, Fructosamine, and HbA1c
(each 75 umol/L change equal about 60 mg/dL or 2% HbA1c)

@GLUCOSE mg/dL	@FRUCTOSAMINE umol/L	@HbA1c %
90	212.5	5.0
120	250	6.0
150	287.5	7.0
180	325	8.0
210	362.5	9.0
240	400	10.0
270	437.5	11.0
300	475	12.0
330	512.5	13.0

Instances where fructosamine may be a better choice than HbA1c include:

- Rapid changes in diabetic treatment – fructosamine allows the effectiveness of diet or medication adjustments to be evaluated after a couple of weeks rather than months.
- Diabetic pregnancy – good control is essential during pregnancy. Fructosamine and glucose levels can help to monitor and accommodate shifting glucose and insulin requirements.
- RBC loss or abnormalities – HbA1c will not be accurate when a patient has a condition that affects the average age of the RBCs present, such conditions include blood loss and hemolytic anemia.

Other blood tests for consideration include (These are associated with endothelial function and will be covered extensively in future lessons):

- Hs-CRP – will usually be elevated due to the inflammatory process (increased cytokine production, in particular interleukin-6)

- Plasminogen activator inhibitor type1 – marker of impaired fibrinolysis. Increased levels are associated with hypercoagulability. Elevated levels correlate with insulin resistance, obesity, hypertension, elevated triglycerides and LDL levels.

- Fibrinogen levels are a reflection of clotting activity. Fibrinogen is also an acute phase reactant, and can be a marker for inflammation and tissue damage. It is a strong and independent cardiovascular risk factor. Plasma fibrinogen has been shown to be increased in type 2 diabetes.

- Urinalysis – ketonuria and glycosuria (indicators of acute decompensation)

- Urine microalbumin – early marker of renal impairment (On dipstick analysis microalbumin will show up about five years before proteinuria)

- Testosterone – Testosterone deficiency is common in men with diabetes, regardless of the type. Testosterone levels are partly influenced by insulin resistance, which may represent an important avenue for intervention, whereas the utility of testosterone replacement remains to be established in prospective trials.[13] A study cited in "The Journal of Clinical Endocrinology & Metabolism", concluded that increasing insulin resistance is associated with a decrease in Leydig cell testosterone secretion.[14] (From a functional medicine perspective, is it better to replace low testosterone by using HRT or get to the root cause, Insulin RESISTANCE?)

- Organic Acids/Oxidative Stress testing – evaluate for mitochondrial dysfunction and oxidative stress.

- Gastrointestinal Stool Analysis – Incretins are peptide hormones that originate in the gastrointestinal tract. The two major incretins are glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP). These hormones are released during nutrient absorption, augmenting insulin secretion.[15] GLP-1 stimulates insulin secretion, cause beta-cell mitosis, inhibit glucagon secretion and delay gastric emptying with an overall anti-diabetic effect. There is recent evidence that suggest a role of the small bowel in the pathophysiology of type 2 diabetes.[16]

- Adrenal Stress Index – all insulin resistance and diabetic patients need to have adrenal function assessed. The major hormones of the body are: adrenalin, cortisol, and insulin, all of which interact with one another. The adrenal glands also secrete DHEA, which has been shown to play a role in prevention and treatment of metabolic syndrome. There are some caveats with the use of DHEA in the treatment of diabetes, one of which is an increase in serum glucose. If you choose to use DHEA, you will need to monitor blood glucose closely.

- Vitamin D (25-OH)- low levels of vitamin D is associated with insulin resistance, beta cell dysfunction, and metabolic syndrome. This is another reason why vitamin D status is a part of basic testing in functional diagnostic medicine.

In Summary

Diagnosing insulin resistance syndrome requires a collaboration of comprehensive patient history, comprehensive physical, nutritional assessment and primary and advanced diagnostic testing. Keep in mind some of the clinical associations of insulin resistance, which include: CVD, polycystic ovary syndrome, low testosterone, and hypertension. All positive lab finding should be assessed at regular intervals (2-4 months) to evaluate the effectiveness of treatment.

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