Functional Medicine University's Functional Diagnostic Medicine Training Program

Module 4 * FMDT 533C

Clinical Application for the Management and Treatment of Diabetes and Insulin Resistance

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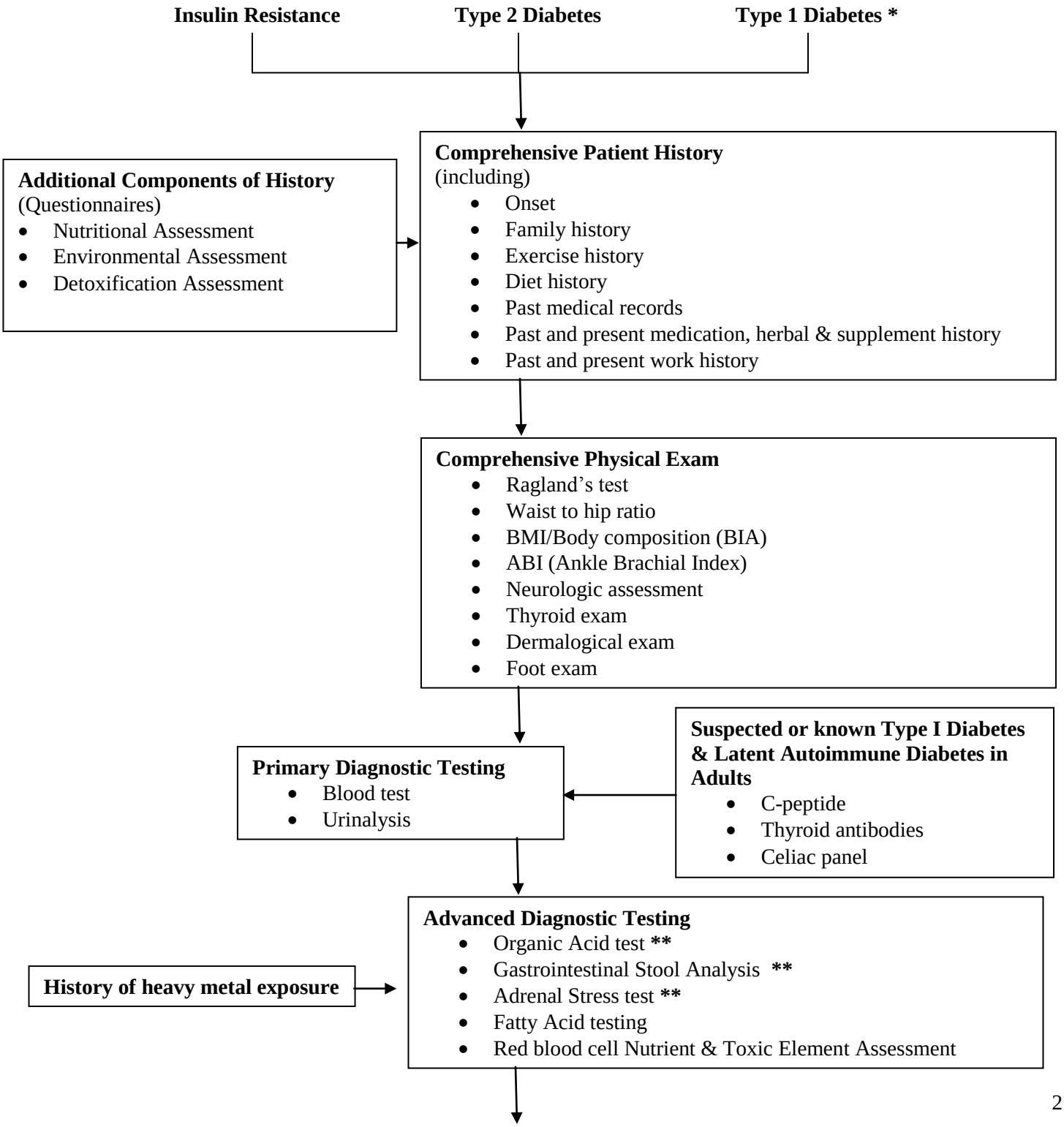
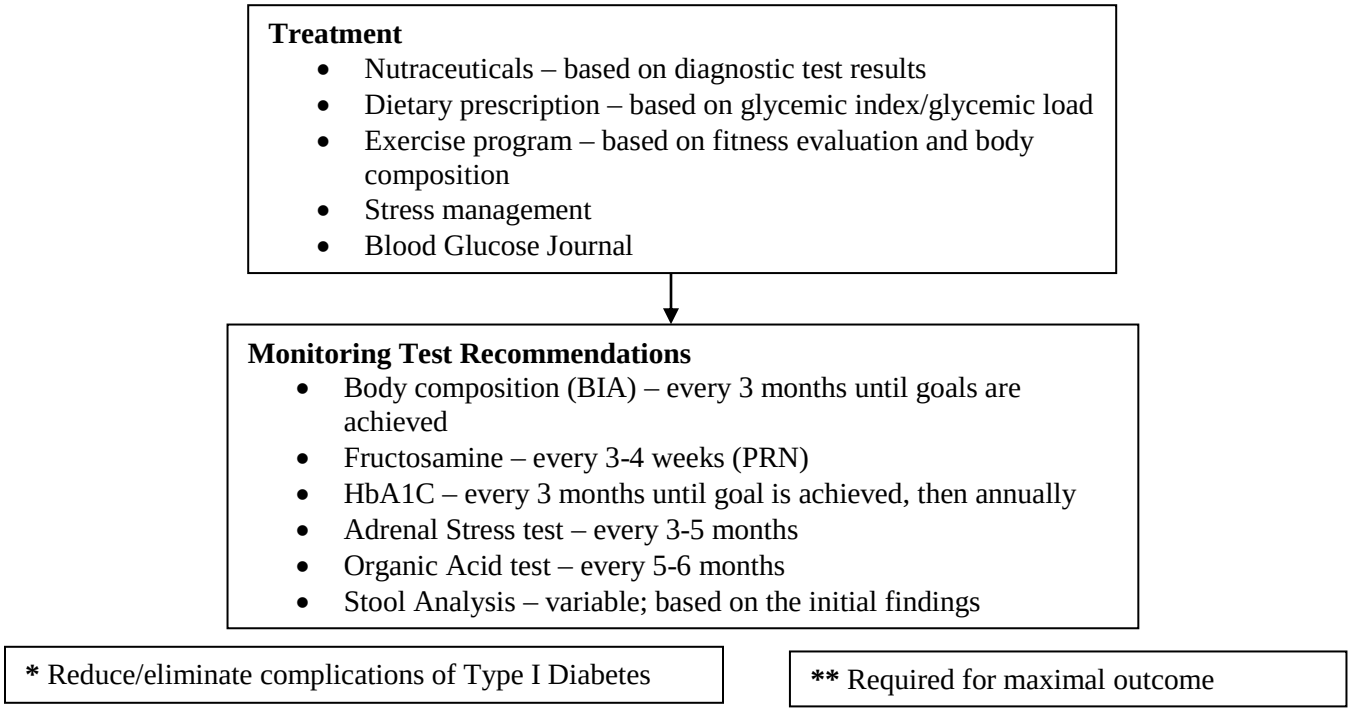
Functional Diagnostic Medicine Approach to Assessment & Treatment of Insulin Resistance, Type 2 Diabetes, and Type I Diabetes *





An understanding of hormonal function is imperative before discussing the clinical applications for the management and treatment of diabetes. Hormones allow the body to interact with the environment and balance the metabolic processes. Hormones act as messengers and interact with each other to allow for the appropriated response to the environment. Epinephrine (adrenaline), cortisol and insulin are the primary hormones that response to environmental inputs. The adrenal hormones, epinephrine and cortisol, mediate the stress response and insulin allows for glucose transport, protein synthesis, fat synthesis, glucose synthesis, and growth and gene expression. The interaction of the major hormone must be kept mind when evaluating all functional medicine patients, and in particular, patients with insulin resistance and diabetes.

The biochemical response to stress includes an increase in the catecholamines, corticotrophin and cortisol. In regard to blood glucose regulation, the action of the sympathetic nervous system facilitates and hastens the breakdown of liver glycogen with subsequent elevation of blood glucose level. Stress also causes an immediate release of ACTH followed within minutes by a significant increase in cortisol. Cortisol is important in resisting stress and inflammation. The effects of cortisol are as follows:

- Stimulation of gluconeogenesis
- Decrease glucose utilization by the cells (Glucocorticoids are believed to depress the oxidation of NADH to NAD^+. Recall that NADH must be oxidized in the process of glycolysis during glucose metabolism.)
- Reduce cellular storage of protein (muscle wasting with chronic excess cortisol. Recall that muscle contract assists with glucose transport into the cells.)
- Increase liver and plasma proteins

- Mobilization of fatty acids (increases free fatty acids into the plasma) [Excess cortisol leads to obesity, in particular, abdominal obesity, which is a part of the metabolic syndrome]

An increase in gluconeogenesis and a decrease in the utilization of glucose cause blood glucose concentrations to rise. This scenario has been referred to as "adrenal diabetes"[6].

The effect of adrenal stimulation is to increase plasma glucose concentration, which in turn cause the pancreas to secrete insulin. The result of high level of insulin secretion, which is called hyperinsulinemia, and high plasma concentrations of glucose (glucose toxicity) is oxidative stress. Hyperglycemia induces the overproduction of reactive oxygen species that increases oxidation of proteins and lipids. Lipid peroxidation decreases membrane fluidity and changes the activity of membrane bound enzymes and receptors. This damage affects every cell of the body and is associated with diabetes, cardiovascular disease and insulin resistance.

High Stress (physical or neurogenic)
↓
↑Epinephrine (Adrenaline)
↓
↑Cortisol levels
↓
↑Insulin levels
↓
Obesity, metabolic syndrome, inflammation, CVD, dyslipidemia

[Keep in mind that the major hormones just described have a significant effect on the metabolism and utilization of the so called minor hormones of the body, which include; progesterone, DHEA, *estrogen (estradiol, estrone and estriol),* testosterone, and thyroid.]

Etiologic classification of diabetes mellitus[2]

I. Type 1 diabetes (beta-cell destruction, usually leading to absolute insulin deficiency)

1. Immune mediated
2. Idiopathic

II. Type 2 diabetes (may range from predominantly insulin resistance with relative insulin deficiency to a predominantly secretory defect with insulin resistance)

III. Other specific types

- **Genetic defects of β-cell function**
  - Chromosome 12, HNF-1α (MODY3)
  - Chromosome 7, glucokinase (MODY2)
  - Chromosome 20, HNF-4α (MODY1)
  - Chromosome 13, insulin promoter factor-1 (IPF-1; MODY4)
  - Chromosome 17, HNF-1β (MODY5)
  - Chromosome 2, *NeuroD1* (MODY6)
  - Mitochondrial DNA
  - Others
- **Genetic defects in insulin action**
  - Type A insulin resistance
  - Leprechaunism
  - Rabson-Mendenhall syndrome
  - Lipoatrophic diabetes
  - Others
- **Diseases of the exocrine pancreas**
  - Pancreatitis
  - Trauma/pancreatectomy
  - Neoplasia
  - Cystic fibrosis
  - Hemochromatosis
  - Fibrocalculous pancreatopathy
  - Others
- **Endocrinopathies**
  - Acromegaly
  - Cushing's syndrome
  - Glucagonoma
  - Pheochromocytoma
  - Hyperthyroidism
  - Somatostatinoma

  - Aldosteronoma
  - Others

- **Drug- or chemical-induced**

  - Vacor
  - Pentamidine
  - Nicotinic acid
  - Glucocorticoids
  - Thyroid hormone
  - Diazoxide
  - β-adrenergic agonists
  - Thiazides
  - Dilantin
  - 10.α-Interferon
  - Others

- **Infections**

  - Congenital rubella
  - Cytomegalovirus
  - Others

- **Uncommon forms of immune-mediated diabetes**

  - "Stiff-man" syndrome
  - Anti–insulin receptor antibodies
  - Others

- **Other genetic syndromes sometimes associated with diabetes**

  - Down's syndrome
  - Klinefelter's syndrome
  - Turner's syndrome
  - Wolfram's syndrome
  - Friedreich's ataxia
  - Huntington's chorea
  - Laurence-Moon-Biedl syndrome
  - Myotonic dystrophy
  - Porphyria
  - Prader-Willi syndrome

- Others

- **Gestational diabetes mellitus (GDM)**

Type 1 Diabetes (absolute insulin deficiency) Insulin-Dependent Diabetes Mellitus

[β-cell destruction leading to insulin deficiency and eventual dependency]

1. Immune-mediated diabetes
2. Idiopathic diabetes (seronegative antibodies and no HLA association; possible genetic mutation of a gene that is essential for the development of the islet cells)

Type 1 diabetes is due to pancreatic beta-cell destruction (islets of Langerhans), predominantly caused by autoimmune destruction. It is theorized that both genetics and environmental factors are involved, however, approximately one-third of the disease susceptibility is due to genetics and two-thirds is due to environmental factors. The major histocompatibility gene complex (MHC), also called human leukocyte antigen (HLA), is a region on chromosome 6 that is densely packed with expressed genes. HLA genes play a major role in a number of autoimmune diseases. About 95% of patients with type 1 diabetes possess either HLA-DR3 or HLA-DR4[1].Other diseases associated with the genetic markers HLA-DR3 and HLA-DR4 include; gluten-sensitivity enteropathy (celiac disease), hyperthyroidism, adrenal insufficiency, myasthenia gravis, and Sjogren's syndrome[1]. Genes designated HLA-DQ are even more specific markers for the possibility of type 1 diabetes. Many drugs can be toxic to the beta-cells and/or impair insulin secretion. Viral infections can trigger diabetes by causing beta-cell destruction. The viruses that have be implicated include; cytomegalovirus, cosackievirus B, and adenovirus. Mumps and congenital rubella have also been implicated.

There has also been much debate about cows' milk triggering diabetes. Research studies suggest a connection of cow's insulin and/or a bovine milk protein called glycodelin and type 1 diabetes. Currently, a pilot study is underway sponsored by the National Institute of Health and Welfare in Finland to assess insulin-free cow milk formula in the prevention of type 1 diabetes associated with autoimmune disease. A recent article in the "Journal of Proteome Research" stated that studies show a causal relationship between cow protein and the risk of onset of type 1 diabetes[2].

Several studies of infant feeding show a causal relationship between time of formula containing cow protein and the risk of onset of type 1 diabetes. B-Lactoglobulin, a major lipocalin in protein in bovine milk, is homologous to the human protein glycodelin, a T cell modulator. Anti-β-lactoglobulin cross-react with glycodelin. The newborn intestine does not have complete "closure" and can pass food antigens. B-Lactoglobulin could generate antibody to glycodelin undermining T cell regulation of the beta cells[2].

Type 1 Diabetes can occur at any age, however, the most common onsets are in children and young adults. The peak incidence is before school age and again at puberty. A majority of patients with type 1 diabetes will demonstrate antibodies to:

- Antibodies to the islets cells (ICA) –[islet antigen-2 antibody]
- Glutamic acid decarboxylase (GAD65) [Antibodies to GAD also exist in "stiff person syndrome". Different epitopes for anti GAD antibodies have been identified in "stiff person syndrome, however a co-morbidity exist with diabetes.GAD is the enzyme that convert glutamic acid to GABA. In stiff person syndrome there is a decrease in GABA.]

- Tyrosine phosphatase (IA-2 and IA2-β)
- Insulin antibodies (IAA)

One author's conclusion was that diabetic antibody testing does not yet have a role in routine clinical care[3]. However, another author stated that these antibodies facilitate screening for an autoimmune cause of diabetes, particularly screening siblings of affected children, as well as adults with atypical features of type 2 diabetes[4].

Selected Autoimmune Antibody Sensitivity and Specificity

ANTIBODY	SENSITIVITY	SPECIFICITY
GAD65	70-90%	99%
insulin	40-40%	99%
Tyrosine phosphatase (IA-2)	50-70%	99%

[NOTE: A new antibody marker was recently discovered called zinc transporter 8. ZnT8A are detectable in a proportion of adult-onset autoimmune diabetes and appear as a valuable marker to differentiate clinical phenotypes[5].]

Symptoms Associated With Type 1 Diabetes

- Polyuria and nocturnal enuresis (look for bed-wetting in children)
- Excessive thirst
- Polyphagia (increased appetite) with weight loss
- Fatigue, weakness and muscle cramps
- Blurred vision (effect of hyperosmolar state on the lens and vitreous humor)
- Gastrointestinal symptoms (nausea, vomiting and/or abdominal pain. Changes in bowel habits (Diabetic ketoacidosis.)
- Slow healing
- Frequent infections

Physical Exam – (see assessment and treatment section)

Diagnostic Testing

- Fasting plasma glucose
- Glucose tolerance test
- HbA1c
- Serum electrolytes
- CBC with iron panel(rule out infection, anemia, hemochromatosis)
- Insulin and C-peptide
- Autoantibodies

- Urinalysis (glucose, ketones and protein)
- Microalbumin/Creatinine (rule out kidney complications)
- Thyroid panel and thyroid antibodies (screen for complication of type 1 diabetes)

Physical Exams and Screening Tests to Consider

- Cardiovascular complication (ABI, lipid panel, ECG, blood pressure)
- Ophthalmological exam (rule out retinal complications)
- Neurological exam (rule out neuropathies)

Treatment of Type 1 Diabetes (Autoimmune and Idiopathic)

Treatment of type 1 diabetes requires a multidisciplinary approach. Insulin is required due to beta-cell destruction and tight glucose regulation is mandatory to prevent complications.

- Insulin therapy (allopathic) The type of insulin prescribed include: fast-acting (onset 5 to 15 minutes, duration 3 to 5 hours), standard insulin (onset 30 to 60 minutes, duration 6 to 8 hours), intermediate insulin (onset 1 to 2 hours, duration 16 to 24 hours), long-acting (onset 1 to 2 hour, durations up to 24 hours) and combinations. Insulin type is usually recommended based on individual blood glucose pattern, exercise habits, other health complications, and food choices.
- Exercise (see treatment for type 2)
- Diet (see treatment for type 2)
- Optimal weight maintenance (BMI/Body composition[BIA] assessment)

Functional medicine considerations

- Preventive care (advise parents about the possible effects of cow's milk. Recommend breastfeeding or alternative feeding formulas. Evaluated for gastrointestinal dysfunction on young children and children nearing puberty. Ask about siblings with type 1 diabetes).
- Oxidative stress testing /organic acid testing (see treatment recommendations for type 2 diabetes) Reactive oxygen species are important mediators of beta-cell death during the development of type 1 diabetes[10, 11].
- Gastrointestinal stool analysis (see treatment for recommendations type 2 diabetes)
- Essential fatty acid testing (see treatment recommendations for type 2 diabetes)
- Stress management (see treatment recommendations for type 2 diabetes)
- Food allergy testing (see treatment recommendations for type 2 diabetes)
- RBC Essential element analysis ((see treatment recommendations for type 2 diabetes)
- Hair/RBC heavy metal analysis (Genetic expression of beta-cell function are influenced by lead and mercury toxicity[9].)

Studies on chemically induced diabetes in mice concluded that zinc supplementation and N-acetylcysteine supplementation were protective in the development of type 1 diabetes [6, 7].Both zinc and N-acetylcysteine inhibited activation of NFkB. Zinc's role as an anti-oxidant was also considered. Another study revealed that high-dose vitamin E supplementation was able to normalize retinal blood flow and creatinine clearance in type 1 diabetes patients[8]. From a

functional medicine perspective, the ability to assess for immune system dysfunction, gastrointestinal dysfunction, hormonal dysfunctional, oxidative stress, and vitamin and essential element status is an integral part of treatment in patients with type 1 diabetes.

Type 2 Diabetes (Insulin resistance to insulin deficiency) 90-95% of cases of Diabetes

- Non-obese (Possible sarcopenia obesity. Body composition testing is required. Consider performing a BIA or similar test)
- Obese (metabolic syndrome/insulin resistance)

Patients diagnosed with type 2 diabetes are not *absolutely* dependent on insulin for life. Insulin therapy may be needed as the disease progresses.

Symptoms Associated with Type 2 Diabetes

Many people have insidious onset and are often asymptomatic. This is particularly true in obese patients. Patient's presenting complaints may be of neuropathic and/or cardiovascular in nature.

- Increased thirst
- Xerostoma (dry mouth)
- Polyuria
- Unexplained weight loss (early)
- Fatigue, weakness
- Headaches
- Blurred vision
- Polyphagia
- Frequent infections (esp. chronic candidiasis) (common sites of infection: bladder, kidneys, vagina, gums, feet and skin) Impotency
- Acanthosis nigricans
- Slow healing
- Paresthesia
- Pruritus (generalized itching)

Physical Examination (see assessment and treatment section)

Diagnostic Testing

Refer to Module 4 * FDMT533B Primary and Advanced Testing: Assessing Blood Glucose Regulation

Oral Pharmaceuticals for Type 2 Diabetes

- Sulfonylureas (glimepiride, glipizide, glyburide)
  - These drugs stimulate the beta cell to secrete insulin. Side effects include; low blood sugar, bloating, nausea, heartburn, anemia, weight gain, sun sensitivity, metallic taste in the mouth

- Meglitinides (nateglinide, repaglinide)
  - These are short-acting insulin secretagogues. They stimulate the secretion of insulin in a shorter time that sulfonylurea drugs. Works quickly when taken with food. (pre-prandial dosing)

- Biguanides (metformin)
  - These drugs reduce the amount of glucose released from the liver. Side effects include; nausea, upset stomach, and diarrhea

- Alpha-glucosidase inhibitors (acarbose, miglitol)
  - These drugs slow the rate of intestinal absorption of glucose. Side effects include; abdominal discomfort, flatulence and diarrhea.

- Thiazolidinediones (pioglitazone, rosiglitazone)
  - These drugs work by increasing activity of receptors that allow for glucose transport into the cells. Adverse reactions include weight gain and peripheral edema

- DDP-4 (dipeptidyl peptidase-4) inhibitors – sitagliptin, saxagliptin)
  - These drugs block the affect of the enzyme DDP-4. DDP-4 breaks down a hormone called glucagon-like peptide-1, whose action is to stimulate insulin release and delay stomach emptying. Adverse effects include; upper respiratory tract infection, urinary tract infection, headaches and pancreatitis.

Drug-Induced Nutrient Depletion [14, 15]

Drug Type	Nutrient Depletion	Mechanism	Potential Depletion Problems
Sulfonylureas	Coenzyme Q10	Inhibition of the NADH-oxidase can lead to a deficiency of Coenzyme Q10	Low energy, CHF, high blood pressure
Biguanides	B_{12} Folic acid	Competitive inhibition of vitamin B_{12} absorption	High blood pressure, CHF, low energy, anemia, cervical

	Coenzyme Q10		dysplasia

The Goal of Functional Medicine Treatment for Insulin Resistance, Type 2 Diabetes, and Type 1 Diabetes

- Insulin Resistance → Eliminate the diagnostic criteria that qualifies the patient with metabolic syndrome/insulin resistance
- Type 2 Diabetes →Eliminate the diagnostic criteria that qualifies the patient with type 2 diabetes and insulin resistance. (eliminate the need for pharmaceutical intervention)
- Type 1 Diabetes → Reduce/eliminate complication of diabetes by assessing for concomitant autoimmune disease, oxidative stress, gastrointestinal dysfunction. Provide educational material about preventive measures.

Functional Medicine Approach to Assessment and Treatment of Insulin Resistance, Type 2 Diabetes, and Type 1 Diabetes

- Comprehensive Patient History (including)

  - Onset
  - Family history
  - Exercise history
  - Diet history
  - Past medical records
  - Past and present medication, herbal and supplement history (assess for drug-induced nutrient depletion)
  - Past and present work history (assess for stress and environment [toxicity] problems)

Use additional components of the comprehensive history as indicated. These would include; environmental assessment questionnaire, nutritional assessment questionnaire, and detoxification questionnaire. Assess for secondary causes of hyperglycemia: pancreatitis, hemochromatosis, pharmacological agents (thiazide diuretics, phenytion, pentamidine, corticosteroids, sympathomimetic drugs, niacin), and liver disease (cirrhosis).

- Comprehensive Physical Examination (including)

  - Vital sign with Ragland's test (Ragland's test assesses for adrenal fatigue)
  - Waist to hip ratio
  - Body mass index and body composition (consider bioelectrical impedance analysis)
  - Ankle brachial index and peripheral pulses (assess for PAD –peripheral vascular disease)
  - Neurological assessment (DTR's, sensation testing, and proprioception testing)
  - Thyroid exam (assess for enlargement, nodules and cysts)

- Skin exam (acanthosis nigricans)
- Evaluate feet for lesions/ulcers

- Primary Diagnostic Testing

  - Fasting glucose
  - Oral glucose tolerance test
  - HbA1c
  - Liver function
  - Comprehensive metabolic profile
  - Lipid panel (VAP Test- A possible early marker of dysfunctional insulin signaling is an alteration of apolipoprotein B and apolipoprotein A serum levels. Apolipoprotein B associates more closely with inflammatory markers and insulin resistance than triglyceride and all cholesterol markers.[17]
  - hs-CRP
  - Vitamin D 25-OH
  - TSH, TT4, TT3
  - Serum insulin
  - Homocysteine
  - Urinalysis (including microalbumin to rule out renal disease, especially in diabetic patients)[microalbumin dipstick are available for in-office testing]
  - Serum testosterone (if clinical indicated)

Additional primary tests to consider if you suspect type 1diabetes or the patient has confirmed type 1 diabetes include:

  - C-peptide
  - Thyroid antibodies
  - Celiac disease panel

- Advanced Diagnostic Testing

  - Organic acid test* – Organic acids are metabolic intermediates that are produced in pathways of energy production, detoxification, biotransformation, neurotransmitter breakdown and intestinal microbial activity. This test can identify metabolic blocks that can be treated nutritionally allowing for individualized nutritional intervention. Organic acid testing assesses fatty acid metabolism, carbohydrate metabolism, citric acid intermediates, B-Complex vitamin marker status, oxidative damage (antioxidant status), and toxicant and detoxification markers.

  - Gastrointestinal Stool Analysis*- Proper gastrointestinal function is critical to adequate nutritional status and can impact all aspects of body function. There is recent evidence that suggest a role of the small bowel in the

pathophysiology of type 2 diabetes.[16] Stool analysis can assess for pancreatic enzyme deficiency, hypochlorhydria, opportunistic and pathogenic bacteria, beneficial bacterial, parasitic infestation, yeast/fungal infestation, and inflammation.

- Adrenal Stress Testing *- This test assesses the status of DHEA and cortisol. Recall that chronic stress can increase blood glucose concentration and thereby, cause hyperinsulinemia. Low levels of DHEA have also been implicated in insulin resistance.

- Fatty Acid Testing – Fatty acids and their metabolic effects have been implicated in the pathogenesis of many diseases, including obesity, diabetes, cancer, heart disease, genetic diseases such as cystic fibrosis, and autoimmune disorders such as rheumatoid arthritis multiple sclerosis. [16] Fatty acid analyses provide useful information about the need for dietary modification and/or fatty acid supplementation. A balance among the essential fatty acids is essential for optimal health.

- Red Blood Cell Nutrient and Toxic Element Assessment –Diabetes is associated with deficiencies of calcium, magnesium, zinc, selenium, and chromium. Genetic expression of beta-cell function are influenced by lead and mercury toxicity.[9]

- Treatment

  - Nutraceuticals – Prescribing nutraceuticals is based on the analysis of primary and advanced diagnostic testing providing an individualize treatment plan.
  - Dietary Prescription – This is mainly based on the glycemic index and glycemic load, and the "eight principles of low glycemic eating".
  - Exercise Prescription – includes a combination of resistance, balance and cardiovascular
  - Stress Management – Stress reduction includes techniques such as meditation, deep breathing, and guided imagery. There are also a variety of relax and meditation CD's that are available. It is also important to address sleep habits and provide recommendation to correct any aberrations.
  - Blood Glucose Journal *(this journal can be found with the Insider's Guide and Handouts for this lesson and in the on-line library at www.FunctionalMedicineUniveristy.com)*

Please review the article in the on-line library titled*: 'National Standard for Diabetics' Self-Management Education'*

- Monitoring Test Recommendations
  - Body Composition –every three months until goal is achieved, then yearly
  - Fructosamine – every 3 to 4 weeks. Testing this often assesses for the effectiveness of treatment and the need for medications.
  - HbA1c – every 3 months until goal is achieved, then yearly
  - Adrenal Stress Re-test – 3 to 5 months
  - Organic acid Re-test – 5 to 6 months
  - Stool Analysis – retesting is variable and is based in the initial finding and treatment

Review of Nutraceuticals and Functional Foods (use advanced functional medicine test result)

- Naringenin
  - The citrus derived flavonoid, naringin, through its correction of many of the metabolic disturbances linked to insulin resistance, represents a promising therapeutic approach for metabolic syndrome. [18] Naringin is one of the major flavones in grapefruit shown to have antioxidant properties. Naringin is hydrolyzed in the intestine, by bacterial action, to naringenin. There is no available research on human trials. Naringin and its metabolite naringenin, have the ability to interfere with liver function by inhibiting some cytochromeP450 enzymes, therefore, it is not recommended in supplement form. It is better to add grapefruit to the diet as a whole food.
- Soluble Fiber
  - Soluble fiber helps reduce post-prandial blood glucose. Soluble fiber is also beneficial in reducing cholesterol levels. Examples of soluble fiber includes: oatmeal, oat bran, fruit, and legumes. Recommendation: 50 to 100 grams combined soluble and insoluble fiber. Increase fiber slowly to attain a therapeutic level. Supplementation may be needed to achieve therapeutic dose level.
- Alpha Lipoic acid
  - Powerful antioxidant as well as a part of the PDC. ALA can enhance glucose uptake and prevent glycosylation. Dose range: 100 to 1,800 mg/ day
- Chromium
  - Chromium is an integral part of insulin signaling. Total body chromium is so low that analytic assessment has limited accuracy. Excess can be assessed by red blood cell analysis. Optimal forms of chromium include; niconate, chloride, histidine or picolinate salts. The form of chromium called GTF, is not effectively absorbed. Food sources include; whole grains, legumes, nuts, yeast and meats. Dosage: 200 to 400 μg/day.
- Vanadium
  - Studies suggest that vanadium has a role in improving insulin sensitivity and abnormal blood lipids. Dosage consideration: 9μg to 125mg/day. Food sources include; buckwheat, parsley, soybeans and safflower oil.
- Magnesium
  - Magnesium plays a role in over 300 enzymatic reactions. Magnesium is required for the formation of active cofactors from vitamins B_1, B_2, B_3, B_5, and B_6. Magnesium has been shown to improve insulin sensitivity. RBC assessment appears to be the best test for magnesium assessment. Food sources include; whole grains, nuts, legumes, molasses and brewer's yeast. Dosage: up to 700mg per day (caution: may cause diarrhea and GI disturbances) Optimal forms include: lactate, gluconate, aspartate and glycinate. Magnesium oxide, carbonate and hydroxide forms are poorly absorbed.

- Vitamin E
  - Vitamin E is an antioxidant and has a role in protecting the plasma membrane from oxidative stress. Dosage; 200 -1,600 IU/day (use mix tocopherols and tocotrienol)

- Vitamin D
  - Has been shown to help with insulin sensitivity as well as immune modulation. Use Vitamin D 25-OH to assess for status. Repletion dosage is based on assessment ranging from 700 to 10,000 IU/day. Reassessment should be done in 2-3 months via blood test.
- Zinc
  - Zinc is necessary for growth and development due to its role in numerous catalytic and regulatory enzymes, and in protein folding and receptor binding. Zinc is involved with the synthesis, storage and release of insulin. The insulin-like effect of zinc, promotion of lipogenesis and glucose transport, seem to be due to inhibition of glycogen synthase kinase 3b. Glycogen synthase kinase 3b is a serine/threonine protein kinase linked with insulin resistance and type 3 diabetes. Zinc is also important for essential fatty acid metabolism. It is needed for the enzyme delta-6-desaturase. RBC analysis appears to be the best test for assessing zinc status. Repletion range is from 5 to 50 mg/day. Zinc completes with copper and cadmium for the same carrier. Copper can be depleted with high dose zinc, use testing for functional assessment.
- Essential fatty acids
  - Omega 3 fatty acids sensitize insulin by acting on PPAR receptors. Essential fatty acids are also part the cell membrane in which the insulin receptor is a part of. I recommend using a balanced formula of EFF's with vitamin E. The use of RBC fatty acid analysis is very helpful in determining nutrient status. Dose range can vary with status; however an average dose of 1.5 grams of omega-3, .75 grams of omega-6, along with mixed tocopherols appears to be the minimal starting dose. (To absorb any oil (fat) the gallbladder must be in good working order. If patient's have had their gallbladders removed, I suggest supplementing with bile salts)
- Cinnamon
  - Cinnamon contains chromium and polyphenols that improve insulin sensitivity. Water-soluble cinnamon extract has been shown to improve body composition and well as systolic blood pressure and fasting glucose levels. (I use Cinnulin PF from Pure Encapsulations: 2 to 3 capsules /day. Each capsule contains 125mg of cinnamon extract.)
- Vitamin C
  - The transport of vitamin C is thought to be facilitated by insulin. Vitamin C is a powerful antioxidant for both intracellular and extracellular reactions and is involved in reactions with reduced iron and copper metallothione enzymes. The synthesis of collagen, carnitine, and neurotransmitters (norepinephrine and 5-hydroxytryptophan) require vitamin C dependent enzymes. Dosage: 1000 to 5000 mg/day.
- Botanicals
  - Botanical that are used to treat diabetes include the following; bilberry, bitter melon, gymnema, ginkgo biloba and fenugreek. The botanical can assist with antioxidant protections and help avoid the

complications associated with insulin resistance and diabetes. Gymnema is noteworthy. Studies suggest that it may have the ability to help regenerate beta cells.

Medical Emergency Treatment[12]

- Hypoglycemia (15:15 rule)
    - Signs and symptoms
        - Diaphoresis, hunger, pallor, anxiety, shakiness, visual disturbances, headache, weakness, dizziness, irritability, nausea, slurred speech, drowsiness, confusion, disorientation, and uncontrolled behavior.
    - Treatment
        - Use carbohydrate sources for oral treatment of mild hypoglycemia. 15 grams of carbohydrate every 15 minutes as needed. Examples of sources: 4 ounces of apple juice; 4-6 ounces of cola or ginger ale (non-diet); 3-4 glucose tablets; 5-7 lifesavers; 2 tablespoons of raisins

    If no improvement, seek medical attention (signs of seizure and coma)

- Hyperosmolar hyperglycemic state
    - Signs and symptoms
        - Excessive thirst, leg cramps, dry mouth, polyuria, tachycardia, weakness and confusion.
    - Treatment
        - HHS is a life-threatening emergency manifested by marked elevation of blood glucose, hyperosmolarity and little or no ketosis[13]. HHS is caused by underlying infections, certain medications, non-compliance, undiagnosed diabetes, substance abuse, and coexisting disease.

- Diabetic ketoacidosis (too little insulin)
    - Signs and symptoms
        - excessive thirst, polyuria, nausea, vomiting, sweat-scented breath, abdominal pain, shallow breathing, elevated blood glucose, loss of appetite, fatigue, weakness, and high ketone
    - Treatment
        - fluid replacement, electrolyte replacement, insulin therapy

Latent Autoimmune Diabetes in Adults (LADA)

Latent autoimmune diabetes in adults is a disorder in which, despite the presence of islet antibodies at the diagnosis, the progression of beta cell failure is slow[20]. LADA is a slowly developing type 1 diabetes which clinically presents as type 2 diabetes (non-insulin dependent diabetes) and progresses to insulin dependence due to positive pancreatic auto-antibodies, in particular GAD (glutamic acid decarboxylase) autoantibodies, destroying the beta cells of the pancreas[21]. Patients with LADA have a high presents of other autoantibodies, which include; anti-TPO (associated with thyroiditis), celiac disease antibodies, and anti-21-hydroxylase (associated with Addison's disease). To date, there are no diagnostic criteria for the diagnosis of LADA. The suggested criteria consist of: between the age of 25 and 65, absence of ketoacidosis or symptomatic hyperglycemia or immediately thereafter, without insulin requirement for 6-12 months, and presence of autoantibodies (especially GADA). From a functional medicine perspective, consider ordering pancreatic autoantibodies if your patient has known celiac disease, thyroiditis and un-resolving adrenal insufficiency, if presenting with signs and symptoms consistence with glucose dysregulation. The gastrointestinal system and the adrenal glands have major influence on the immune system. This is another reason why ordering a stool analysis and an adrenal stress test are a part of the evaluation and treatment of insulin resistance and diabetes.

Type 3 diabetes

The "Journal of Diabetes Science and Technology" November of 2008 reviewed evidence of Alzheimer's disease and what they called "type 3 diabetes". The research revealed that there are disturbances in brain insulin and insulin-like growth factor signaling mechanisms that account for the majority of molecular, biochemical and histopathological lesions in AD.

*Transient Electromagnetic Field*s

Other research suggests that there in a connection between transient electromagnetic fields (dirty electricity) and elevated blood glucose levels among pre-diabetics and diabetics. Dirty electricity is generated by electronic equipment and wireless devices (foot note). To reduce exposure dirty electricity, it was recommended to avoid exposure and/or install GS filters (Graham-Stetzer). This type of increased blood glucose has also been referred to as "type 3 diabetes".

Dietary and Exercise Prescriptions

There will be two videos in the inflammation module dedicated to dietary and exercise recommendations.
These videos will outline patient specific dietary guidelines and exercise prescriptions that are realistic for patient compliance and highly effective for optimal treatment outcomes.

Environmental Toxins: A Potential Risk for Diabetes

There appears to be a growing consensus that environmental factors may be linked to diabetes. Dr. Walter Crinnion, an authority in environmental medicine, stated "eliminating toxins can also reverse one of the most troubling conditions that's on the rise: diabetes'. Diabetes has been associated with having persistent organic pollutants in the body. You will learn how to assess and manage toxicity in the module on detoxification.

In Summary

You now have the tools to assess and manage insulin resistance, type 2 diabetes and type 1 diabetes. Follow the assessment and treatment protocol outlined in this course; *excluding the required advanced functional medicine testing will greatly decrease favorable outcomes.* Remember, keeping the diet and exercise recommendations simple and user friendly will assist with patient compliance. It's a good idea to schedule your patient at least one time per week for the first four weeks of care. This minimizes the patient from becoming overwhelmed with too much information at once and allows the patient time to adjust to any necessary lifestyle changes that you have recommended, thus increasing the likelihood of optimal clinical outcomes.

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