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MARK HYMAN, M.D.



How To Work With Your Doctor

To Get What You Need

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Introduction:

Why You Need This Guide

Though there is much you can do to treat yourself for diabesity, working with a doctor experienced in a comprehensive approach to treating this problem is essential. Having a good relationship with a primary care physician and undergoing regular evaluations is critical in monitoring your treatment. However, there is one problem. The vast majority of physicians practicing today are not familiar with the methods I outlined in *The Blood Sugar Solution*. Some may not take a truly comprehensive approach to diagnosis and treatment of diabesity or be aware of or order the appropriate panel of tests. Others may not test you at all unless you have progressed down the path of disease. And *most* doctors interpret tests quite differently than I do, taking a "wait and see approach," which can be dangerous.

Getting an Annual Physical Examination

You will need to have a regular physical examination so your doctor can monitor important potential complications related to diabesity, including elevated blood pressure, cataracts, early nerve damage, kidney dysfunction, joint damage, as well as indications of heart disease and dementia. I also **strongly** encourage you to work with a doctor to get a basic, baseline set of tests that can help you understand more precisely how severe your imbalances are and exactly what is going on inside your body, and provide a way of tracking your progress and improvement.

Special Note: Blood Pressure

Blood pressure is a simple but indirect measure of insulin resistance. In fact, insulin resistance causes 50 percent of all high blood pressure. Ideal blood pressure is less than 115/75. Over 140/90 is significantly elevated. The other major undiagnosed cause of high blood pressure is sleep apnea. Properly treating insulin resistance and sleep apnea will often result in a "cure" of high blood pressure or hypertension.

In addition to having an annual physical examination and getting the right tests from your primary care physician, you should have an annual ophthalmologic (eye) exam to check for early signs of eye damage that can lead to blindness. Diabetic foot exams are also critical because the loss of sensation may lead to injury and ulcers, which can lead to amputations. These are not typically complications of insulin resistance, but must be monitored in diabetics.

As you now know, treating diabesity early and intensively is essential if you want to halt or reverse its progress. Getting your physician to assist you in this process by providing you with the correct tests and assessments is critical.

That is why I have developed this guide. In it you will find:

- A complete list of tests I recommend for the assessment of diabesity and related conditions, including indications on how to properly read those tests
- Testing and additional medical treatments that are available for imbalances in the 7 steps
- A letter you can give your doctor that outlines the principles of Functional medicine and why this approach is essential in the treatment of diabesity

If you cannot get your primary care physician to cooperate in your treatment the way you want, you may need to consider looking for another doctor. However, it is my hope that with the tools in this guide you can work with your doctor to get the assistance you need. Good health care is a team effort between patient and doctor. I hope you can find someone you can work with to help you reverse your diabesity. (See the Resources section of *The Blood Sugar Solution* for information on how to find a practitioner of Functional or integrative medicine.)

Tests for Diabesity:

Looking for Causes and Seeing the Effects

Let's start by reviewing a list of tests and treatment options that are available to you when you work with a doctor. Understanding what tests to ask for will help you advocate for yourself in your doctor's office and the broader medical setting.

To do the tests recommended here and get the care you need, you will most likely have to find an experienced practitioner of Functional or integrative medicine. Most conventional doctors simply will not give you these tests. I offer some recommendations on places to find practitioners of functional and integrative medicine in the Resources section of *The Blood Sugar Solution*.

You can also visit our team at **The UltraWellness Center** in Lenox, Mass. Please see our website for more information (<u>www.ultrawellnesscenter.com</u>) or call us at (413) 637-9991. Physician visits must be done in person. Nutrition consultations can be done by phone. We also offer two discounted special month-long healing programs: **Achieving UltraWellness** and **Achieving an UltraMind**. These can be done in person or through phone consultations.

Most tests I recommend in my practice are available through conventional large commercial labs such as Quest Diagnostics or LabCorp. Other tests are available through small specialty labs that specialize in metabolic, immune, nutritional, or functional testing. After each test discussed below, I have given recommendations on which lab or labs to use to obtain the test.

There is still great controversy in conventional medicine circles about the utility of these laboratory tests, but I have used them with great success for more than 20 years on thousands of patients to help me navigate this new medical territory. Rather than provide "on or off" types of diagnoses—you have this or you don't—they provide a picture of where you are on the continuum from optimal health to full-blown disease.

Many of these tests identify disturbances in function, not pathology. In other words, you might not have anemia from lack of folate, but you might have any number of important pathways that are jammed because you don't have enough folate for you and that may lead to cancer, dementia, depression, heart disease, or birth defects.

The tests I recommend often help me identify patterns and guide me in choosing the best therapies to help my patients achieve optimal health. I think they can help you and your doctor in the same way.

While extensive testing isn't always necessary, basic testing can be **very** helpful in homing in on specific imbalances in your biochemistry that are creating problems for you.

A number of laboratory tests may be useful in helping you identify your degree of insulin resistance, the severity of your diabesity, its complications, underlying causes, or contributing factors. I have divided these into two groups. The Basic Diabesity Tests help assesses the presence and severity of diabesity. The Additional Tests for Diabesity help determine the degree of dysfunction or problems that result from or contribute to diabesity, including inflammation, kidney and liver function, thyroid and sex hormone function, or nutritional deficiencies. In Chapter 17 on specialized testing for the underlying causes of diabesity, I will review the tests that help identify the underlying causes of diabesity, based on imbalances in the 7 key systems in the body. These tests help uncover specific nutrient deficiencies, food allergies, pesticide or heavy metal exposure, gut dysfunction, and more.

These Basic and Advanced tests are ALL readily available from any doctor or laboratory, and they are important for screening for, evaluating, and monitoring diabesity. Most are available from Quest Diagnostics or LabCorp. If you have never had them done, do them all. If you have had recent tests, you can do these yearly or more often as recommended by your doctor to evaluate your progress. During the first year or two I recommend repeating these tests every four to six months.

The specialty tests need to be selected based on consultation with a Functional or integrative physician, and need to be monitored and evaluated less frequently based on your individual needs and condition.

Testing Laboratories

Quest Diagnostics <u>http://www.questdiagnostics.com/</u> A resource for most conventional laboratory testing needs.

LabCorp

<u>https://www.labcorp.com/wps/portal/</u> A resource for most conventional laboratory testing needs.

LipoScience

<u>http://www.liposcience.com/</u> Innovative nuclear medicine spectroscopy for the assessment of lipid particle size and improved accuracy in assessing cardiovascular risk factors.

Doctor's Data

<u>http://www.doctorsdata.com/home.asp</u> Experts in testing for heavy metal toxicity and other nutritional and metabolic disorders.

Metametrix

<u>http://www.metametrix.com</u> Leaders in nutritional and metabolic testing.

Genova Diagnostics

<u>http://www.gdx.net/</u> Leaders in nutritional and metabolic testing and genetic testing of SNP—singlenucleotide polymorphisms—to help identify disease predispositions that can be modified with lifestyle interventions.

Immunolabs

http://www.immunolabs.com/patients/ IgG food sensitivity testing.

Prometheus Labs

<u>http://www.prometheuslabs.com/</u> Leaders in testing for gluten-related disease.

DiagnosTechs http://www.diagnostechs.com Testing for adrenal stress hormones.

IGeneX

<u>http://igenex.com/Website/</u> Specialized testing for detecting chronic infections such as Lyme disease with PCR technology.

Melisa

<u>http://www.melisa.org/laboratories.php</u> Testing for the toxic immunological effects of mercury and other heavy metals.

Basic Diabesity Testing: To Diagnose Presence of Diabesity

- Insulin response test—fasting, 1-hour, and 2-hour glucose and insulin levels after a 75-gram glucose load. Hemoglobin A1c (abnormal is > 5.5% of total hemoglobin).
- NMR lipid profile—particle size and number of LDL, HDL, and triglycerides. You should have fewer than 1,000 total LDL particles and fewer than 500 small LDL particles (the dense, dangerous type). This test is performed by Liposcience, but can be ordered through LabCorp, a laboratory testing company. Total cholesterol/HDL ratio. Abnormal is greater than 3.Triglyceride/HDL ratio (Abnormal is > 4)
- Total cholesterol/HDL ratio (> 3)

Additional Tests for Diabesity: To Assess Severity of Complications of Diabesity

- High-sensitivity C-reactive protein (abnormal > 1.0 mg/liter) to assess inflammation.
- Fibrinogen (abnormal > 350 mg/deciliter) to assess clotting risk and thick blood.
- Lipoprotein (a) (abnormal > 30 nmol/L) to assess treatable genetic cholesterol marker.
- Uric acid (abnormal > 7.0 mg/dl) to assess gout risk caused by diabesity.
- Liver function tests (elevated AST, ALT, GGT are abnormal) to assess fatty liver.
- Kidney function tests (BUN (abnormal > 20 mg/dl), creatinine (abnormal< 1.2 mg/dl)) to assess kidney function.
- Microalbumin (abnormal > 20 mg/dl) to assess protein in urine, an early marker for damage to kidneys.
- 25 OH vitamin D (abnormal < 45–60 ng/dl) for vitamin D status
- Homocysteine (abnormal > 8.0 micromoles/liter) a sensitive marker for folic acid deficiency.
- Ferritin (abnormal > 200 ng/ml) to assess inflammation and iron status.
- Thyroid hormones (TSH, free T3, free T4, TPO antibodies)*
- Sex hormones (male and female)* DHEAS, estradiol, progesterone, free testosterone, and sex hormone binding globulin) to assess sex hormones.

* See Step #2 in Chapter 9 for thyroid and sex hormone testing information.

Explanation of Basic Testing for Diabesity

Blood Glucose: Is Measuring Your Blood Sugar Helpful?

Historically, diabetes was diagnosed when one's fasting blood sugar level was higher than 140 mg/dl. Now we recognize diabetes complications happen at much lower blood sugar levels. That's why the cutoff was recently lowered to 126 mg/dl. In the past, a blood sugar level higher than 110 mg/dl was considered glucose intolerance; now it is 100 mg/dl. Why do we keep moving the goal posts? Because we are learning that what we thought was normal was not really normal. You still get sick at what were previously considered normal blood sugar levels. The real question is: What is the optimal level of blood sugar? It turns out it is much lower than we thought.

A remarkable study published in *The Journal of the American Medical Association* found that anybody with a blood sugar level higher than 87 mg/dl had an increased risk for type 2 diabetes.ⁱ This study was done in young healthy men in the military. It was startling, because it found the lowest risk for diabetes is a blood sugar level of lower than 81 mg/dl. I believe we will see that any blood sugar level between 80 mg/dl and 100 mg/dl signals a problem and an increased risk for diabetes and insulin resistance.

The "normals" we typically have in medicine may not be "normal." They may be normal for a sick population. If 65 percent of Americans are overweight, then the "normal" weight for Americans is fat! The increasing loads of dietary sugars and the spikes of insulin they produce increase your risk of cardiovascular disease even if you don't have diabetes. You can even have a perfectly "normal" blood sugar level and still be at risk.

That is why the insulin response test described below is so critical to diagnosing diabesity. The only problem is that most doctors do not know how to do or interpret this test. Even with a normal fasting blood sugar level, if your insulin is high, you can have many of the problems and complications associated with diabetes, particularly heart disease, stroke, dementia, and cancer.

Therefore, we must look at the basic laboratory tests in more detail with a new light in order to identify how to interpret them most effectively.

Insulin Response Test

Most physicians perform a glucose tolerance test to evaluate diabetes. However, by the time your blood sugar goes up in the typical glucose tolerance test, you are far down the continuum of disease and insulin resistance and are already in big trouble. The conventional oral glucose tolerance test, or OGTT, will often miss many, many cases of sugar or insulin problems.

There are six stages of diabesity or insulin resistance. Most doctors only act when people reach the fifth stage. The Blood Sugar Solution provides a plan of action right from the first stage.

- 1. The first stage of insulin resistance is high spiking levels of insulin 30 minutes, one hour, and two hours after the introduction of a sugar load. Your blood sugar may stay completely normal in these time frames.
- 2. The second stage is elevated levels of fasting insulin with a perfectly normal blood sugar level while fasting *and* after a glucose challenge test.
- 3. The third stage is the elevation of blood sugar and insulin after the glucose drink at 30 minutes, one hour, or two hours.
- 4. The fourth stage is an elevation of your fasting blood sugar level higher than 90 or 100 mg/dl and elevation of fasting insulin.
- 5. The fifth stage is the elevation of your blood sugar level higher than 126 mg/dl.
- 6. The sixth stage is decreasing insulin levels and pancreatic burnout with increasing levels of blood sugar.

The insulin response test is probably the single most important test in all medicine to learn your risk of diabesity, heart disease, cancer, dementia, and premature death. It is cheap, easy, and any lab can do it, yet it is almost never done.

The test I recommend is a two-hour glucose tolerance test, with measurements of insulin and blood sugar checked after taking a 75-gm load of sugar (the equivalent of two sodas). You first measure fasting glucose and fasting insulin levels. Then you take the sugar drink and measure glucose AND insulin 30 minutes, one hour, and two hours later. Recent studies have identified fasting and the 30-minute insulin and glucose test as a sensitive alternative to the two-hour test to diagnose insulin resistance. Some people have a delayed insulin response, but the 30-minute test can be a quick way to do the test for most people.

There are no agreed upon "normals" for these tests, but after doing more than 5,000 of them over 15 years, I can share with you what I think is optimal and ideal.

Blood Sugar Levels

- Fasting blood sugar should be less than 80 mg/dl.
- Thirty-minute, one-hour, and two-hour glucose should not rise above 110 mg/dl; some say 120 mg/dl.

Insulin Levels

- Fasting insulin should be between 2 and 5 mIU/dl; anything greater than 10 mIU/dl is significantly elevated.
- Thirty-minute, one-hour and two-hour insulin levels should be less than 25 mIU/dl to 30 mIU/dl. Anything higher than 30 mIU/dl indicates some degree of insulin resistance.

The insulin response test is the most sensitive test available to identify insulin resistance and diabesity very early on and highlights the need for more aggressive approaches to treatment and care. It can also be useful in patients with diagnosed diabetes to see if they are still capable of producing insulin or if they have burnt out their pancreas. This can influence treatment recommendations. In some cases even a burnt-out pancreas can recover and diabetes can be reversed. For some, after decades of beating up their bodies with a toxic diet and lack of exercise, it may not be possible to reverse diabetes completely. But we can effectively treat everyone and prevent further complications with a comprehensive approach.

Hemoglobin A1c

Checking just one blood sugar reading doesn't tell you much about your overall blood sugar control. There is a test called *hemoglobin A1c*, or *glycosylated hemoglobin*, that can tell you if your overall blood sugar has been high over the previous six weeks. This test is used in monitoring diabetics but has now been proposed as a better way of diagnosing diabetes than just a random fasting blood sugar test.

Even in the face of normal fasting blood sugar your hemoglobin A1c can be high, because it measures your average sugar, including the effects of all the food you eat throughout the day. I use it to screen for overall blood sugar balance. Ideally it should be less than 5.5 percent of total hemoglobin. Anything higher than 6.0 is considered diabetes. Higher than 7.0 is considered poorly controlled diabetes.

Blood Cholesterol Testing

Conventional treatment for cholesterol focuses only on lowering LDL cholesterol with statins. We measure and treat LDL because it is what we have the best drugs treat, not because it is the most important marker of your risk of heart disease. In fact your LDL cholesterol is a very bad predictor of your risk of heart disease when compared with the total cholesterol-to-HDL ratio. And this is not as good a predictor as the triglyceride-to-HDL ratio (which incidentally is the best way to check for insulin resistance other than the insulin response test).

In fact, according to a paper published in *Circulation,* the most powerful test to predict your risk of a heart attack is the ratio of your triglycerides to HDL. If the ratio is high, then your risk for a heart attack increases 16-fold—or 1,600 percent!ⁱⁱ This is because triglycerides go up and HDL or good cholesterol goes down with diabesity.

Very often patients with diabesity have normal LDL and total cholesterol, but very high triglycerides and very low HDL. For example, it is not uncommon to see patients with triglycerides of 300 mg/dl and HDL of 30 mg/dl. This is much more of a concern to me than someone with total cholesterol of 300 mg/dl and LDL of 140 mg/dl but triglycerides of 60 and HDL of 80. So assessing triglycerides and HDL is critical.

Optimal Cholesterol Levels

- Total cholesterol < 180 mg/dl
- LDL cholesterol < 70 mg/dl
- HDL cholesterol > 60 mg/dl
- Triglycerides < 100 mg/dl
- Total cholesterol/HDL ratio < 3.0
- Triglyceride to HDL ratio < 4

Unfortunately, the old way of testing cholesterol can lead to deceptive conclusions. You may have a totally normal total and LDL cholesterol but be at very high risk of a heart attack because it is the wrong type of cholesterol. In fact, more than 50 percent of people who show up in the emergency room with heart attacks have normal cholesterol. But they have small cholesterol particles, which are caused by insulin resistance. Let's look a little more deeply at the question of how to properly measure cholesterol.

Specialized Cholesterol Testing: Size Matters

Newer tests look at not only the total amount of cholesterol, but also the actual size of the cholesterol particles as well as the total number of cholesterol particles. In my view this is the only test for cholesterol that should be performed. Using older versions of cholesterol testing leads to practicing medicine with blinders on. It is outdated, misleading, and often leads to harmful prescriptions for medication when not indicated. It can also provide a false sense of security when your cholesterol numbers are normal but the type of cholesterol you have is the small, dangerous kind.

The newer cholesterol test I recommend is called *nuclear magnetic resonance spectroscopy*, or *NMR lipid testing*. It is performed by a laboratory called LipoScience. LabCorp will also send blood to that lab for analysis when asked. This test is a much more sensitive, more precise indicator of your risk of heart disease than the total cholesterol or LDL cholesterol numbers you get from a regular blood test.

Studies have found that people who have a cholesterol level of 300 mg/dl but have very large cholesterol particles have very little risk of cardiovascular disease. On the other hand, people with a "normal" cholesterol level—such as 150 mg/dl—but very small and numerous LDL and HDL cholesterol particles have an extremely high risk of heart disease.

But what causes these small dangerous cholesterol particles? It is the sugar and refined carbohydrates in our diet. Insulin resistance causes these small cholesterol particles to form, and taking statins won't fix the problem. The NMR test for cholesterol is one of the most essential tests in evaluating the degree of insulin resistance and cardiovascular risk. Smaller particles are dangerous. They act like BB pellets, damaging arteries and putting your health at greater risk. Light, fluffy beach ball–like cholesterol particles, on the other hand, are harmless and bounce off arteries regardless of the overall LDL cholesterol number.

Optimal NMR Tests

- Total LDL particles < 1000 nmol/L
- Total small LDL particles < 600 nmol/L
- LDL size > 21 nm
- HDL size > 9 mmol/L
- VLDL < 0.1 nmol/L

Additional Tests for Diabesity

Measuring the insulin response test and the NMR lipid test will quickly help to determine your level of diabesity. They are the most important, but other tests that measure cardiovascular risk are also important in filling in the picture of just how severe a problem you have and what to do about it. You should also get the following tests:

- **High-sensitivity C-reactive protein** (less than 1.0 mg/L is ideal): This is the best measure of hidden inflammation in the body.
- **Fibrinogen** (less than 350 mg/dl is ideal): This is a clotting factor in the blood that increases with inflammation and insulin resistance.
- Lipoprotein (a) is a genetically inherited lipoprotein marker that increases the risk of cardiovascular disease but can be treated. Less than 30 nmol/L is ideal.
- **Uric acid** (less than 7.0 mg/dl is ideal): This is a byproduct of protein metabolism that causes gout and an increase in insulin resistance.
- Homocysteine (less than 8.0 mol/L is ideal): This is a sensitive marker for folic acid deficiency.
- **Ferritin** (less than 200 ng/ml is ideal): This is a measure of excess iron stores that increases with inflammation and insulin resistance.
- **Liver function tests** (elevated AST, ALT, GGT): These tests identify the death of liver cells, most often caused by elevated insulin resistance because of a fatty liver.
- **Kidney function tests** (BUN, creatinine, and microalbumin): Used to identify early damage to kidneys, which can occur even without full-blown diabetes.
- **25 OH vitamin D** (45-60 ng/dl is ideal): Vitamin D deficiency is an important predisposing factor to diabesity.
- **Thyroid hormones** (TSH, free T3, free T4, TPO antibodies): Low thyroid function worsens and often occurs with diabesity.
- Sex hormones (male and female): These hormones are often altered by diabesity and are important to monitor and treat.

Inflammation: Cause and Effect in Diabesity

Among the tests above, the two most important are C-reactive protein, which measures inflammation, and liver function, which measures liver damage from inflammation, something that is very common with insulin resistance. C-reactive protein is significantly elevated in most people with diabesity. As the diabesity gets better the inflammation goes down.

Fatty Liver: Toxicity in Diabesity

One of the major complications of diabesity is *fatty liver*, also known as *nonalcoholic steatohepatitis*. It affects up to 70 million Americans and is the number one cause of liver damage in this country. Think about it—you can get hepatitis from eating too much sugar and too many flour products! The French delicacy *fois gras* (which means "fatty liver" in French) is made by force-feeding ducks starchy carbohydrates (corn), which turns to sugar. The sugar is what turns to fat in our livers, creating problems with detoxification, which leads to a further increased load of toxins in our bodies, creating more disease in a vicious cycle. That is why it is important to measure liver function with AST, ALT, and GGT tests and treat the liver to reverse this problem.

Kidney Function: Early Signs of Damage

Early signs of kidney damage are important to evaluate. The best way to do this is through a *microalbumin* test, which measures small amounts of protein in the urine. You also should measure BUN and creatinine as overall indicators of kidney function.

Optimal Levels

- Microalbumin: <2 0 mg/dl
- BUN: < 20 mg/dl
- Creatinine: < 1.2 mg/dl

Vitamin D: A Key Factor in Promoting Diabesity

Get tested for 25 OH vitamin D. The current ranges for normal are 25–137 nmol/L or 10–55 ng/ml. These are fine if you don't want to get rickets, but not enough for optimal health. The

range should be 100–160 nmol/L or 40–65 ng/ml. In the future, we may even raise this "optimal" level further. In fact, I like my patients to be between 60–80 ng/ml.

Monitor your vitamin D status until you are in the optimal range. If you are taking high doses (5,000 to 10,000 IU a day), your doctor must check your calcium, phosphorous, and parathyroid hormone levels every three months.

Hormonal Imbalances: Common in Diabesity

Thyroid Dysfunction

People with diabesity often have problems with thyroid function, and it is often undiagnosed. I recommend checking TSH, free T3, free T4, and thyroid peroxidase antibodies as the baseline tests to assess thyroid function. For more information on thyroid function testing, see *The UltraThyroid Solution* at: www.bloodsugarsolution.com/ultrathyroid

Make sure you get the following tests:

- TSH (ideal range is between 1 and 2): This is a measure of the pituitary hormone that controls the thyroid.
- Free T3 and free T4: These are a measure of the circulating thyroid hormones.
 - The normal level of free T4 is usually between 0.9 and 1.8 ng/dl.
 - The normal level of free T3 is considered to be between 240 and 450 pg/dl, depending on the laboratory measurements. However, the reference ranges for laboratory tests are often based on "normal populations." (Remember "normal" means the average of population, not necessarily the ideal.)
- TPO (thyroid peroxidase) and antithyroglobulin antibodies: These are autoimmune antibodies in the thyroid gland that interfere with its function. They should both be less than 20 IU/ml.

Sex Hormones

I recommend checking *free and total testosterone* in men, which is often low in insulin resistance and diabetes. This leads to muscle loss, fatigue, loss of motivation, low sex drive, and impotence.

I also recommend checking *DHEA-S* measurement of adrenal function as well as total and *free testosterone and estrogen and progesterone*, FSH (follicle stimulating hormone), and

LH (luteinizing hormone) between days 18 and 23 of the menstrual cycle for premenopausal women and anytime for postmenopausal women. These are very helpful in identifying imbalances of hormones, which are common in diabesity. Women often have increased levels of testosterone and DHEA-S and a ratio of LH/FSH (luteinizing hormone to follicle stimulating hormone) of > 3:1.

Optimal Levels of Hormones

Men:

- Total testosterone: > 500 ng/dl
- Free testosterone: > 20 pg/dl

Women

- Free testosterone: < 0.5 to 5 pg/dl
- DHEA-S: < 200 mg/dl
- LH/FSH ratio: < 3:1
- Estradiol (depends on age and time of cycle)
- Progesterone (depends on age and time of cycle)

Getting these tests will help you understand the nature and severity of your health risks associated with diabesity. Work with your doctor to get them all done so you both know what you are dealing with. It will inform your treatment, and they offer a good measure for how much you heal using *The Blood Sugar Solution*.

Specialized Testing for the Underlying Causes of Diabesity

Identify Imbalances in the 7 Steps

In addition to the basic evaluation outlined in the previous chapter, a number of other tests can be helpful in identifying the underlying causes of diabesity and monitoring its effects and improvement with treatment. These tests may be needed depending on how you score on the "7 Steps Quiz" in your *Six-Week Action Guide*.

If your score qualified you for medical care in any one of the 7 steps, you should start the Basic or Medical Care plan and add on any additional self-care steps that are recommended in Part II of *The Blood Sugar Solution*.

After the first six weeks of the program have been completed, retake the self-assessment in *The Six-Week Action Plan* for any of the steps in which you had a severe imbalance. Many of you may no longer show a severe imbalance after you have completed the first six weeks of the plan; however, if you do, please seek out the assistance of a practitioner of integrative or Functional medicine and work through the tests and treatments in this chapter and the one that follows.

In this chapter I want to focus on the testing available for imbalances in the 7 steps specifically. Then, in the next chapter we will discuss some medical treatment options you can pursue with your physician.

The tests I recommend include tests for nutritional status, hormonal balance, food sensitivities or allergies, gluten sensitivity, digestive imbalances, toxins including petrochemicals and heavy metals, mitochondrial function and oxidative stress, and the effects of stress on your body. First let me provide you with a simple list of the most important tests you need, and then we will discuss each of them in more detail below.

Overview of Important Testing for Imbalances in the 7 Steps

Step #1: Boost Your Nutrition: Nutritional Testing

- Magnesium Quiz
- RBC minerals (including chromium and vanadium)
- Vitamin D Quiz
- EssentialOmega-3 Fatty Acids testing
- OAT or organic acid testing

Step #2: Regulate Your Hormones

- Thyroid Quiz: TSH, free T3, free T4, TPO antibodies
- Sex Hormone Imbalance Quiz
 - Male: total and free testosterone
 - Female: FSH, LH, estradiol, progesterone, free testosterone, DHEA-S

Step #3: Reduce Inflammation

- Gluten allergy/celiac disease testing (all these tests help identify various forms of allergy or sensitivity to gluten or wheat)
 - IgA antigliadin antibodies
 - IgG antigliadin antibodies
 - o IgA antiendomysial antibodies
 - Tissue transglutaminase antibody (IgA, and IgG in questionable cases)
 - Total IgA antibodies
- IgG food sensitivity (special antibody tests against common foods)
- Elimination/provocation: This is simply removing potentially allergic foods like gluten and dairy for two weeks, then reintroducing them and monitoring how you feel. My book *The UltraSimple Diet* describes a comprehensive elimination diet in great detail.
- Testing for hidden infections: This specialized testing needs to be ordered by a trained physician of functional or integrative medicine.

Step #4: Improve Your Digestion

- Gut immunology: EPX and calprotectin stool analysis
- Digestion Quiz
- Gut ecology and digestive stool analysis
- Urine organic acid dysbiosis analysis

Step #5: Maximize Detoxification

- Provoked urine toxic element test: Levels of heavy metals (mercury, lead, arsenic, antimony, etc.)
- Toxity Quiz
- Blood levels of PCBs, solvents, pesticides, and heavy metals
- Urine organic acid or OAT testing for detoxification

Step #6: Enhance Energy Metabolism

- Urine organic acid (OAT) testing for mitochondrial function
- Energy Metabolism QuizUrinary 8 OHDG for Oxidative Stress or Rusting QuizLipid peroxides
- VO2 max: cardiometabolic stress testing

Step #7: Soothe Your Mind

• Stress and Adrenal Fatigue Quiz

Now let's look at all these tests in a little more detail. For each step I will outline the name of the tests I recommend and labs where they can be ordered. I will also provide details about what the test is and how it is useful in examining the optimal levels your doctor should be looking for with you.

Step #1: Boost Your Nutrition: Nutritional Testing

There are common nutrient deficiencies that promote the development of diabesity. The most important to assess are chromium, magnesium, vitamin D, and essential fatty acids. People with diabesity often have magnesium, chromium, and vitamin D deficiency.

Essential fatty acids (omega-3 fats) are critical in normal blood sugar control and insulin function. And more than 90 percent of Americans are omega-3 fat deficient. Simply supplementing with omega-3 fats improves blood sugar control, reduces triglycerides and improves HDL, and lowers inflammation. However, there can be unusual fatty acid problems that specific tests may be helpful in uncovering.

Here are the tests I recommend to assess problems with any of these nutrient levels:

Magnesium Testing

Quest Diagnostics, LabCorp, Metametrix, or Genova Diagnostics

Serum magnesium is most often used but is rarely helpful. Levels of less than 2.0 can be significant.

Red blood cell magnesium is more accurate (nl 4–6), but if you have symptoms of magnesium deficiency, the best way to know if the addition of magnesium to your diet will help is to try taking it and seeing how you feel.

Red Blood Cell Minerals

Metametrix or Genova Diagnostics

Mineral status is a critical part of nutritional health. This can identify deficiencies or imbalances in many minerals including chromium and vanadium.

Essential Omega-3 Fatty Acid Testing

Metametrix or Genova Diagnostics

It may be useful to test red blood cell fatty acid levels to look for the proper balance of fats, especially low levels of omega-3 fats and high levels of omega-6 fats. This test can identify essential fatty acid deficiencies as well as excesses of inflammatory fats and trans fats.

OAT (Organic Acid Test): Urine Organic Acids

Metametrix or Genova Diagnostics

Organic acids are byproducts of metabolism. They are helpful as a general nutritional and metabolic screening test. They help identify vitamin B deficiencies, including biotin, which is important in diabesity, as well as problems with fat, carbohydrate, and energy metabolism. They also help with oxidative stress, the gut, detoxification, and even neurotransmitter function. This is probably the single best-advanced test for evaluating diabesity because it covers so many problems with the 7 steps.

Step #2: Regulate Your Hormones

These tests are all included in the basic testing for diabesity because hormones are so important. I include a little more explanation here.

Testing for Thyroid Dysfunction (Part of Basic Testing for Diabesity) *Quest Diagnostics, LabCorp, or Genova Diagnostics*

There is no one perfect way, no one symptom or test result, that will properly diagnose low thyroid function or hypothyroidism. The key is to look at your symptoms and your blood tests, and then decide.

Doctors typically diagnose thyroid problems by testing your TSH levels and sometimes your free T4 level. But some doctors and researchers have brought the normal levels of those tests into question.

The diagnosis of "subclinical" hypothyroidism depends on having a thyroid-stimulating hormone (TSH) level higher than 5 mIU/L and lower than 10 mIU/L. But new guidelines from the American College of Endocrinologists suggest that anything higher than 3 mIU/L is abnormal. This number is an improvement but still may miss many people who have normal tests and a malfunctioning thyroid system.

To get a complete picture, I recommend looking at a wider range of function:

- TSH (ideal is between 1 and 2 mIU/L).
- Testing for free T4 (ideal level is 1–1.4 ng/dl) AND free T3 (ideal level is 300–400 pg/dl), which are the inactive and the active hormones.
- Thyroid antibodies (TPO) or autoimmune thyroid antibodies. Most doctors don't check this UNLESS the TSH is high. This is a big mistake. Many people have autoimmunity against their thyroids, which makes it function poorly, but still have "normal" TSH. That's why I think this should be part of routine screening.
- Basal normal body temperature is 98.6 degrees F. This is measured with a special basal body thermometer you can obtain at a pharmacy. Check your temperature before getting out of bed in the morning. If you are a menstruating woman, check it

only between the first and third days of your menstrual cycle (the first day is the first day of bleeding).

Testing for Sex Hormone Imbalances (Part of the Basic Tests for Diabesity)

Testing for sex hormone imbalances in women is tricky because levels change throughout the menstrual cycle. Postmenopausal testing is easier. The best time to test for hormones in premenopausal women is anywhere between days 18 and 23 of the menstrual cycle. For postmenopausal women, anytime is fine. Hormone testing is essential to monitor the effects of bio-identical hormone replacement.

Women's Hormone Testing (Blood)

Quest Diagnostics, LabCorp, or Genova Diagnostics

- 1. FSH (follicle stimulating hormone)
- 2. LH (luteinizing hormone)
- 3. Estradiol
- 4. Progesterone
- 5. SHBG (sex hormone binding globulin)
- 6. Free testosterone
- 7. DHEA-S

Men's Hormone Testing

Quest Diagnostics, LabCorp, or Genova Diagnostics

- 1. Free testosterone
- 2. Total testosterone

Note that saliva testing is an accurate, noninvasive way of measuring sex hormone levels and can be used to measure variations over time by measuring at different times of the menstrual cycle.

Step #3: Reduce Inflammation: Find the Causes of Inflammation

Gluten testing and food sensitivity or IgG testing can be very helpful in identifying sources of inflammation from your diet. Selective use of IgG food sensitivity testing can identify low-grade food allergies and sensitivities. Eliminating food sensitivities that cause inflammation can reduce systemic inflammation and its effects on insulin and blood sugar. Here are the tests I recommend.

Gluten Allergy/Celiac Disease Testing

LabCorp or Quest Diagnostics

Each of these tests helps identify various forms of allergy or sensitivity to gluten or wheat. Remember, gluten sensitivity exists all the way along the continuum from mild sensitivity to full-blown celiac disease. I recommend that anyone with any level of antibodies or autoimmune reaction to gluten do a six-week, 100 percent gluten elimination. Stopping and then reintroducing it is the ONLY way to really know how gluten affects you:

- IgA antigliadin antibodies
- IgG antigliadin antibodies
- IgA antiendomysial antibodies
- Tissue transglutaminase antibody (IgA, and IgG in questionable cases)
- Total IgA antibodies
- HLA DQ2 and DQ8 genotyping for celiac disease (used occasionally)

IgG Food Sensitivity (Special Antibodies Tests against Food)

Immuno Laboratories or Genova Diagnostics

While still controversial, well-controlled studies have shown that these tests are helpful in identifying problem foods. Removing these foods helps inflammatory problems. I have found these tests to be imperfect though helpful guides in locating trouble foods.

Elimination/Provocation

This is simply the process of removing potentially allergic foods like gluten and dairy from your diet for two weeks, then reintroducing them and monitoring how you feel. *The Blood Sugar Solution* has a six-week gluten and dairy elimination and provocation test built into it. My book and home study course, *The UltraSimple Diet*, describes a more comprehensive elimination diet if you need it.

Special Side Effects

Following a short-term comprehensive elimination diet often leads to extraordinary side effects including relief from many health problems such as arthritis, autoimmune diseases, migraines, fatigue, allergies, irritable bowel syndrome, and much more.

Hidden Infections

Quest Diagnostics, LabCorp, Medical Diagnostic Laboratories, or IGeneX Labs

You can have a chronic, smoldering infection that leads to an activation of your immune system and promotes system-wide inflammation. If inflammation persists despite changing your diet and lifestyle, taking supplements, and addressing food allergies and insulin resistance, then you may have a hidden infection. There are many tests that identify hidden infections.

Step #4: Improve Your Digestion: Digestive Functioning Tests

Occasionally if there is systemic inflammation and you have ruled everything else out, the gut can be a source of hidden problems.

General Gut Health, Bacterial Balance, and Parasite Testing: Stool Analysis for Dysbiosis

Metametrix, Genova Diagnostics, or Doctor's Data

Many chemical markers in the stool can be analyzed to give a picture of the ecosystem. Markers for digestion, absorption, acid-alkaline balance, as well as cultures of various bacteria, yeasts, or parasites can often pinpoint the sources of inflammation and be linked to many diseases. Some conventional labs do test for parasites but are often not experienced and miss many infections. Newer tests even assess the DNA of microbes in the gut through PCR testing of the entire gut ecosystem and can identify the balance of good and bad bugs in the gut.

PCR Stool Testing for Gut Ecology

Metametrix

This test is an innovative way to identify hard-to-find bacteria, yeasts, parasites, and worms, which can trigger systemic inflammation.

Urine Organic Acid Test (OAT) for Bacterial and Yeast Metabolites

Metametrix or Genova Diagnostics

Organic acids are metabolites in the urine that can give clues to nutritional status, but the organic acid test is often used to look at unusual chemicals that come from the gut, such as

bacteria, yeasts, or parasites. The test can be helpful in identifying problems and tracking treatment, but even a negative test doesn't rule out significant imbalances in the gut. Currently we can measure only some of the activity, not all of it.

Step #5: Maximize Detoxification: Identifying Hidden Toxins

A number of tests are available that can assess petrochemicals and heavy metals as well as their effects on our detoxification system. There are also tests to assess our genetic detoxification capacity.

The most important test is a *urine toxic element test*. This is a simple test that measures stored heavy metals in the body. It is done by orally taking a chelating agent such as DMSA or DMPS, followed by a six-hour urine collection.

This test measures the total body load of heavy metals. Measuring simple blood tests or an unprovoked urine test doesn't reflect total body burden. Using these methods will not give you a clear assessment of the amounts of metals in your body. Most doctors just check blood levels, and if they are fine they think everything is fine. Nothing could be further from the truth. The metals are cleared from the blood in 30 to 90 days after exposure, and while some are eliminated in stool and urine, many get stored in your tissues and organs, including the liver, kidney, and brain. The provoked urine test is the only clinically available measurement of your total body heavy-metal burden.

There are also newer tests available to measure the levels of solvents, PCBs, and pesticides in the blood. This can help uncover ongoing exposures to chemicals and diagnose toxininduced diabesity. Here is what I recommend.

Heavy-Metal Testing Overview

These tests can be critical in identifying heavy-metal poisoning. If you are concerned about heavy metals, you should find a doctor of Functional medicine and have these tests performed. If you have many amalgam fillings, regularly consume seafood, get flu vaccines, or live in an area close to coal-burning industrial plants or medical incinerators, then you should be tested for mercury and other heavy metals.

Chelation Challenge

Doctor's Data or Genova Diagnostics

The chelation challenge test is often better than any other test at identifying the levels of heavy metals. An FDA-approved chemical chelation agent called DMSA (challenge dose is 30 mg/kg) can be used to mobilize the metals that are found in a 24-hour urine sample that is collected and sent to the lab. DMPS, sold over the counter in Germany and used widely in Europe and Russia, is another well-used chelating agent that can be used for testing or treatment. The challenge dose is 250 mg for children and 500 mg for adults. It is not FDA approved but is legally available from compounding pharmacies in the United States.

Whole Blood or Red Blood Cell Heavy-Metal Levels: Lead, Mercury, Arsenic, Etc. *Quest Diagnostics, LabCorp, Doctor's Data, Metametrix, or Genova Diagnostics*

Even though this is the test used by conventional doctors to screen for metals, it is ONLY accurate in picking up very recent exposure (the last 120 days) because most of the toxic metals are cleared quickly from your bloodstream and are stored in your tissues and bones for decades.

Urinary Organic Acids

Metametrix or Genova Diagnostics

Specific compounds can be measured, including sulfates, pyroglutamate, orotate, and others, that can give clues to problems with detoxification pathways. This can be useful for anyone scoring high on the detoxification quiz.

Chemical Testing

I rarely perform chemical tests because I assume nearly everyone has some degree of chemical toxicity. Body burden studies have been done through the Environmental Working Group (www.ewg.org) and the Centers for Disease Control and Prevention (www.cdc.gov/exposurereport) and have found hundreds of chemicals in everyone. For more serious or acute exposures, certain tests that identify chemicals can be helpful. For example, blood levels of PCBs, solvents, and pesticides can be tested. You can order these tests through Metametrix.

Step #6: Enhance Energy Metabolism: Identifying Loss of Energy and Oxidative Stress

We can test for mitochondrial function and oxidative stress, which is very important in diabesity. We can identify the effectiveness of fat and carbohydrate metabolism and

cellular energy production as well as important markers of free radical or oxidative stress damage. Here is what I recommend.

Specialty Testing for Mitochondrial Function

While the tests above cover many general factors that affect your energy production, such as toxins, allergens, infections, poor diet, and nutritional deficiencies, the following tests focus specifically on mitochondrial function and can be important in cases where this is a potential problem. The most important test is the organic acids test (OAT).

Urine Organic Acids Test

Metametrix or Genova Diagnostics

The body produces many byproducts of metabolism. We can measure these in the urine after the body excretes them. The tests can identify metabolic weak spots or deficiencies. They are a great way to look at the function of mitochondria. With them, we can see how fats and carbohydrates are processed through the mitochondria, and even how well the mitochondria make energy.

If there are steps in your energy production system that are not functioning properly, we can identify the steps and the exact nutrient, cofactor, or amino acid necessary to correct the problem.

For example, if you have trouble getting fats into your cells for energy, we know you may need more carnitine, an amino acid that transports fats into the cells. Then we can prescribe carnitine to help overcome the problem. This is an overnight urine test.

Cardiometabolic Stress Testing: VO2max

This is a special cardiac stress test that measures how much oxygen you can consume or burn per minute. It is directly related to your mitochondrial function and your fitness level. The lower the level, the higher your risk of death. People with diabesity have much lower capacity to burn oxygen and calories in their mitochondria and have much lower levels of V02max, which can be corrected with interval training and mitochondrial nutrient support. This test is often only available from specialists in exercise physiology, although I think it is an excellent way to learn about the mitochondria and monitor fitness levels and improvement in function.

Oxidative Stress Testing: Damaged DNA Byproducts

Metametrix or Genova Diagnostics

This tests for 8 OHDG or 8-hydroxy-2-deoxyguanosine found in the urine. It is usually done by specialized labs. Testing indicates the presence of oxidized or damaged DNA, which is closely connected to neurologic diseases.

Oxidative Stress Testing: Lipid Peroxide Assays in Urine or Serum or TBARS *Metametrix or Genova Diagnostics*

This provides indicators of rancid or oxidized fat in the body, especially the fats from our cell membranes. It is an excellent indicator of oxidative stress.

Step #7: Soothe Your Mind

Here are the tests I recommend you discuss with your doctor to assess your stress level.

An Adrenal Stress Index

DiagnosTechs or Genova Diagnostics

This is a measure of four separate saliva tests for cortisol done at four different times of the day. A number of labs perform this test, which helps you identify if your stress response is still functioning normally, if you are on overdrive, or if you are burned out. Each finding may require different treatment.

Heart Rate Variability

When you are stressed, your body and brain are less resilient, flexible, and complex. They get stuck in rigid patterns of function, behavior, and mood. One of the best ways to measure this is the "flexibility" of your heart rate.

A small device hooked up to a computer can record very minute changes in your heartbeat from second to second. The more complex and variable your heart rate, the healthier your autonomic nervous system, which controls both the stress response and the pause button. Heart rate variability is something you can change almost instantly by changing your breathing or thinking. And it can even be measured at home using a simple software program and sensors for your fingers. There are two products I recommend that are wonderfully effective:

- Healing Rhythms by Wild Divine
- emWave by HeartMath

Now that we have covered the tests you need, in the next chapter we will review some of the medical treatments available to help you rebalance these key systems in your body.

Medical Care for the 7 Steps

Once you have procured the necessary tests to identify imbalances in the 7 key systems in your body, the next step is to pursue medical treatment options that will help you rebalance these steps. In this chapter I will review some of the options available. Note that for each step I have only chosen a few of the most important and effective treatments available. Many other options exist. Discuss the possibilities with a practitioner of Functional or integrative medicine.

Step #1: Boost Your Nutrition

One of the foundational concepts of Functional and systems medicine is **biochemical individuality.** We are all different with slightly different needs and imbalances. Nutritional testing helps to identify weak or trouble spots in your biochemistry and fix them as needed. Your physician can further customize your treatment based on nutritional testing. Here are a few things that are particularly important in diabesity:

- Testing for amino acids and neurotransmitters can help identify your particular imbalances more accurately.
- Further customization of amino acid therapy is possible based on testing and your symptoms.
- Testing for omega-3 fats, vitamin D, magnesium, zinc, chromium, and selenium can be helpful in identifying the need for additional supplementation.
- Testing for methylation problems with homocysteine and methylmalonic acid is often very helpful in optimizing doses of folate, B12, and B6.

Step #2: Regulate Your Hormones

Choosing the Right Thyroid Hormone Replacement

Ultimately, to properly balance a thyroid that is severely out of balance, you will need to go on some type of thyroid hormone replacement therapy. There are certain things you can do by altering your diet and your lifestyle, but if your thyroid isn't functioning properly you may need to have some additional thyroid hormones to supplement its output. Knowing what's available and what to ask about can empower you to make better decisions about your health.

A combination of experience, testing, and trial and error is necessary to get it just right. However, I have found that the majority of my patients benefit from a combination hormone treatment including T4 and T3.

Synthroid, the most commonly prescribed thyroid hormone, is just T4, the inactive hormone. Most doctors assume that the body will convert it to T3 and all will be well. Unfortunately, pesticides, stress, mercury, infections, allergies, and selenium deficiencies can block that process. Since 100 percent of us have stored pesticides in our bodies, we will all likely have some problem with Synthroid.

The most common treatment I use is Armour thyroid

Armour thyroid is a whole combination of thyroid hormones including T4, T3, and T2ⁱⁱⁱ (a little known product of thyroid metabolism that actually may be very important). There are other ways of obtaining combinations of T4 and T3, including compounded desiccated porcine thyroid (like Armour) or compounded bio-identical T4 and T3. I sometimes even use combinations of prescription T4, such as Levoxyl or Synthroid, along with prescription T3 called Cytomel.

Armour is a prescription drug made from desiccated or dried porcine thyroid. It contains the full spectrum of thyroid hormones including T4, T3, and T2. It seems paradoxical that taking a pig hormone can make your brain better, but it does. The right dose ranges from 15 to 180 mg, depending on the person.

Many doctors still hold the outdated belief that the preparation is unstable and the dosages difficult to monitor. That was true with the old preparation of Armour, not the new one. (See <u>www.armourthyroid.com</u> for more information). It has been increasingly difficult to obtain Armour thyroid, but it may become more widely available in time. It is my preferred treatment for thyroid dysfunction. It is the best treatment for about 80 percent of my patients. The rest need some combination of prescription or compounded thyroid.

Sometimes the only way to find out if you have a thyroid problem is a short trial of something like Armour thyroid or equivalent for three months. If you feel better; your symptoms disappear; your mood, memory, and behavior improve; and you have more energy and lose weight (assuming this a problem for you, which it is for many people with a thyroid

deficiency), it's the right choice. Occasionally, further customization of thyroid hormones is necessary using various combinations of T4 and T3 in prescription or compounded forms.

Once started it doesn't have to be taken for life (a common misperception). Sometimes, once all the factors that disturb your thyroid have been corrected, you may be able to reduce or discontinue the dose.

As with any treatment, always work with an experienced physician in using medications for your thyroid. Careful monitoring is essential. Taking too much thyroid hormone, or taking it if you don't need it, can lead to undesirable side effects including anxiety, insomnia, palpitations, and, over the long term, bone loss.

WARNING

If your adrenal glands are burned out from long-term stress, treating the thyroid without supporting the adrenal glands through relaxation and adaptogenic herbs (such as ginseng, rhodiola, or Siberian ginseng) can actually make people feel worse. Your Functional or integrative medicine practitioner will know how to balance your adrenal glands before treating your thyroid with medication.

Bio-Identical Hormone Replacement

Occasionally, despite lifestyle therapies, diet, exercise, stress reduction, nutrient supplementation, and herbs, sex hormone therapy may be the answer.

A physician knowledgeable and experienced with bio-identical hormone therapy must prescribe them. The ONLY hormones that should be used are ones that are identical to those made by your body. They have very specific actions when they bind to their hormone receptors on your cells. Synthetic or animal hormones typically have unwanted side effects and dangers.

For menopause your doctor may try:

- Topical combinations of estradiol, estriol, progesterone, and testosterone, which are prepared by compounding pharmacies
- My approach is to use the lowest dose possible to relieve symptoms, to use only bioidentical hormones and to use them topically (vaginal, skin, under the tongue)
- Oral hormones should be used with as low a dose as possible and only when topical hormones are not effective
- DHEA supplementation, which can be helpful sometimes

For severe cases of PMS not improved by diet, lifestyle, or supplements, your doctor may try:

• Topical, natural, bio-identical progesterone in the last two weeks of the menstrual cycle; the usual dose is ½ tsp (20–40 mg) applied at night to thin skin areas of your body during the last two weeks of the menstrual cycle

For men's hormone balance your doctor may use:

- Testosterone—topical is ideal after measurement of your hormone levels and with ongoing monitoring of testosterone and PSA levels
- DHEA supplementation

Step #3: Reduce Inflammation

Once testing has been completed, specific treatments for infections or more aggressive treatments for autoimmunity and allergies may be needed. Discuss this possibility with your doctor.

The most important triggers of inflammation are our diet, hidden allergens and gluten, hidden infections, digestive imbalances, environmental toxins, and stress. Each of these has specific treatments.

Cleaning up your diet and following *The Blood Sugar Solution* will take care of most of the dietary causes of inflammation. A more comprehensive gluten and food allergy elimination diet, which I describe in my book *The UltraSimple Diet* (www.bloodsugarsolution.com/ultrasimple-diet) and the associated home study course called *Kick-Start Your Metabolism in 7 Days: The UltraSimple Plan to Quickly and Safely Lose Up to 10 Pounds* (www.bloodsugarsolution.com/ultrasimple-challenge) is sometimes necessary.

Intensive gut healing (see Step #4) is also very important in addressing one of the most important sources of systemic inflammation.

Sometimes finding and treating low-level toxins such as mercury and lead can be essential in reducing inflammation.

Occasionally, odd hidden infections, including hidden dental infections in old root canals or hidden viral or bacterial or tick-borne infections, can be a source of chronic inflammation. These need to be "hunted down" and treated on an individual basis.

Finally, learning to find the pause button and reduce the effects of chronic stress can cool the fires of inflammation for many.

Each person is unique, and many need specific treatments for the cause of inflammation that include the use of antimicrobials like antibiotics or antifungals and chelating agents. An experienced practitioner of Functional or integrative medicine will recommend these treatments as needed. The key thing to remember is that it often takes persistence and diligence to find the source of the inflammation and treat it directly. But with time this can be done and is remarkably more effective than anti-inflammatory medications such as steroids, Advil-like medications, or immunosuppressive or immune-blocking medications. And with much fewer side effects.

Step #4: Improve Your Digestion

Very often some simple dietary changes and supplements can help overcome years of digestive problems. However, this is an area in which it is often helpful to have some testing and to work with a doctor of Functional medicine who knows how to address work with digestive problems.

The healing process takes four main steps, which have to be done in the right order for you to get the best results. This is often referred to as the **4 R program**:

- **Remove** any offending factors, including potential food allergens; overgrowth of bacteria, yeast, parasites, and worms; and toxins, such as heavy metals.
- **Replace** missing or weakened enzymes, digestive acids, and fiber or prebiotics in order to help fertilize the healthy bacteria.
- **Re-inoculate** with probiotics or beneficial bacteria.
- **Repair** the intestinal lining with healing nutrients.

Eliminating allergens and taking enzymes, prebiotics, probiotics, and healing nutrients can be done without medical care, EXCEPT if you have a significant overgrowth of bacteria in your small intestine, yeast overgrowth, infestation with parasites or worms, or heavy-metal toxicity. Testing is often needed to identify these problems. Then medication is often needed for adequate treatment. Sometimes herbs can be helpful in reducing the bad bugs. So you can try working to fix your gut on your own, but if things don't improve, it may be time for testing and medication with your doctor's help.

Remember, if you are standing on a tack, it takes a lot of aspirin to feel better. If you have too much bacteria, yeast, or a parasite, you can eliminate all the foods you like or add all the healthy bacteria, but it may be an uphill battle unless you fully address any imbalances or infections with bugs in the gut.

Special Note: Treating Bugs

Bugs that affect the gut come in four main varieties:

- Bacteria
- Yeast
- Parasites
- Worms

Each type of bug needs a different treatment. Testing can identify which bug or bugs are a problem for you.

Herbal therapies can often be helpful, but most of the time a short course of curative medication is necessary and is dramatically effective.

Guidance from a trained practitioner is often necessary to test for and treat these problems.

Step #5: Maximize Detoxification

In a medically supervised detoxification program, many nutrients, herbs, and phytonutrients may be used, including alpha lipoic acid, NAC, milk thistle (which are already part of *The Blood Sugar Solution*), bioactive whey protein, and amino acids such as taurine, glycine, glutamine, calcium-D-glucarate, and methionine. Detoxification is a powerful method of healing when applied carefully and intelligently. It is one of the most powerful tools to restore optimal health and may, in fact, be a major target in the future treatment of diabetes as we learn more about the impact of toxins on our weight and metabolism.

Special Note: Detoxifying from Heavy Metals

Detoxifying from heavy metals is an important step on the road to health for many and needs to be done with an experienced and qualified health care practitioner.

Aside from addressing hidden food allergens and helping people balance their blood sugar and consume a whole-foods diet, one of the most powerful ways to correct many chronic health problems is a medically supervised heavy-metal detoxification program. Proper testing, preparation, and care are needed in order to achieve safe and effective heavy-metal detoxification. Below you will find the steps I often recommend to prepare my patients for heavy-metal detoxification. I will also outline the options available for treatment.

I want to reinforce that this **must** be done with a qualified health care practitioner.

Below I describe the most important steps to help prepare you for safe metal removal. Once you have improved your health and optimized your detoxification system, you can begin working to remove metals from your body through various approaches including safe amalgam or silver-filling removal (see <u>www.iaomt.org</u>) and the use of chelating agents such as DMSA, which is a prescription medication designed and approved for lead removal in children, but also effective against mercury and many other toxic metals.

While there needs to be more research done in this area, the current body of evidence, my experience, and the experience of thousands of other doctors and patients make it clear to me that this can be a critical part of the process of healing for chronic illnesses, including diabesity.

To read an excellent consensus position paper on heavy-metal detoxification called "Defeat Autism Now!" that was developed by a group involved with autism treatment, go to www.autism.com/triggers/vaccine/heavymetals.pdf.

Recognize that there is much controversy in this area as well as many opinions on the best way to detoxify from heavy metals. I humbly offer my hard-won and personal observations and knowledge on how to do this safely and effectively.

Getting Ready for Detoxification

These are the general guidelines I use with my patients that I recommend you follow with your doctor. They should generally be done in collaboration with your health care provider and may take a few months.

• First, optimize your gut function by eliminating common food allergens and taking probiotics and enzymes for one to two months before detoxifying.

- Optimize your nutritional status for detoxification using healthy fats (omega-3 fats, olive oil, and flax oil); the amino acids noted above (which boost your liver's detoxification capacity); and minerals, particularly zinc and selenium (which help your body detoxify metals).
- Enhance your liver's detoxification pathways—especially the sulfation and methylation pathways—by taking folate, B12, and B6; eating foods that contain sulfur, such as broccoli, collards, kale, daikon radish, garlic, onions, and omega-3 eggs; and supplements such as alpha lipoic acid and N-acetylcysteine.
- Use herbal support for heavy-metal detoxification, including alginate, cilantro, garlic, and milk thistle.
- Start sauna therapy and make sure that you take adequate electrolyte and mineral replacements to prevent dehydration and mineral loss from the perspiration.
- Optimize elimination routes for metals through your urine, stool, and perspiration by drinking plenty of clean pure water, eating a diet high in plant fibers, and taking daily saunas for 30 minutes.

Once you have prepared for the process of detoxification using the steps above, you can then begin detoxifying from heavy metals by using chelating agents. However, you must work with an experienced physician to do this.

Step #6: Enhance Energy Metabolism

Once testing has been completed, your doctor may recommend additional supplements for helping support your mitochondrial function including creatine, coenzyme Q10, carnitine, alpha lipoic acid, NADH, magnesium, B vitamins such as riboflavin or niacin, NAC, sulfate, and reduced glutathione. Resveratrol derivatives or extracts are also powerful mitochondrial energy boosters and are in drug development now (Sirtris was just purchased by Pfizer). Note that many of these supplements are already built into *The Blood Sugar Solution.*

Your doctor may also prescribe additional energy-boosting treatments and exercises such as interval training. If you haven't already begun interval training, now is the time. It's an excellent way to boost your energy metabolism.

Step #7: Soothe Your Mind

Occasionally, hormonal treatment with DHEA or low-dose cortisone or additional herbal therapies can be helpful if you have adrenal burnout. Acupuncture and traditional Chinese medicine are also very powerful in helping restore the adrenal system balance and correct the effects of chronic stress.

But ultimately, finding your "pause button" is up to you. Focused practice of deep relaxation and restorative self-care in the form of meditation, yoga, breathing practices, or qigong, as well as things such as massage, hot baths, saunas, journaling, and engaging in regular rhythmic living with consistent times of waking, eating, and sleeping are very helpful in restoring our natural biological rhythms and righting the hormonal chaos of chronic stress.

By using the self-care strategies in *The Blood Sugar Solution* and the tests and medical treatments outlined in this guide, you and your doctor should be able to isolate and treat the underlying imbalances in your physiology that are driving your illness. Once you do, you will begin to experience what it is like to be vibrantly healthy. Good luck!

Letter and Other Information for Your Doctor

It is important that you form a partnership with your doctor. The old model of medicine was "the doctor knows best". Trust the doctor and take this pill. In the past when there wasn't much doctors could do for patients besides give them hope and an aspirin that was probably the best way to engage the healing response. The biology of belief is very powerful. But today, with medical knowledge exploding and with increasing specialization, you have to be the CEO of your own body and health. But you also need expert advice and help. You can ask questions, inquire about new tests or treatments, ask about research, and be fully engaged in your care. That is how you can best create health for yourself. Remember, your doctor is trained in disease and illness, not health and wellness. Treating a symptom is different than treating your whole system. You are responsible for your whole system. *The Blood Sugar Solution* provides you with the knowledge and tools you need to heal your whole system, but you may need your doctor's help.

With that in mind I compiled the materials in this chapter to help you better communicate with your doctor. It includes:

- A letter you can copy and give your doctor that outlines the principles of *The Blood Sugar Solution*
- A quick-reference list of diabesity tests
- An editorial I wrote that will help them better understand the Functional medicine model of treating diabetes
- A complete list of medical references from *The Blood Sugar Solution*

In order to best partner with your doctor to get the tests and treatments outlined in *The Blood Sugar Solution* and in this guide, try photocopying these materials and giving them to your physician. I hope it helps convince your medical practitioner to join in the revolution that is happening in medicine today.

Dear Doctor:

In my practice, I have found the diagnosis and treatment of diabesity (the continuum of insulin resistance from metabolic syndrome to diabetes) to be one of the more rewarding aspects of patient care. Diabetes and metabolic syndrome combined affected well over 100 million Americans and close to 1 billion people worldwide. According to research published in *Diabetes Care* in December 2009, the diabetic population will rise to 44.1 million in 2034, from 23.7 million now, with medical spending increasing to \$336 billion from \$113 billion.

Double the patients, triple the cost. Clearly what we are doing to treat this pandemic is not adequate. Early diagnosis and comprehensive treatment is necessary to stem this tsunami of disease and its social and economic burden. Insulin resistance is also a major underlying process that contributes not only to diabetes, but also to most cardiovascular disease, dementia and most common cancers.

The phenomena of insulin resistance and diabetes emerges from the interaction of genetic predispositions and environmental insults—our highly-refined, processed, high-sugar, low-fiber, high-fat diet; our sedentary lifestyle; chronic stress; and, increasingly, environmental toxins.

Over the last few decades the mechanisms of explaining how these gene-environment interactions lead to disease have become clear. Our toxic diet, lifestyle, and environment trigger secondary phenomenon of nutritional deficiencies, inflammation, oxidative stress, mitochondrial dysfunction, digestive imbalances, hormonal dysfunction (thyroid and sex hormone) and effects of environmental toxins such as persistent organic pollutants and heavy metals on metabolism.

These underlying mechanisms lead to the clinical phenomena we treat: hyperglycemia, hypertension, hyperlipidemia, and coagulopathy. However, these "numbers" are simply **risk factors**, clinical indicators that are downstream from the **real causes**. And treating risk factors alone will not address the underlying systemic causes that drive insulin resistance. We need to move beyond risk factor management to treatment of the causes of the disease.

The real causes are our 21st century diet, sedentary lifestyle, chronic stress, and environmental toxins. Addressing these upstream causes in a comprehensive and systematic program will correct the mechanisms (inflammation, oxidative stress, mitochondrial dysfunction, etc.), which in turn will resolve the risk factors that we treat hyperglycemic, hypertension, and hyperlipidemia. What we do now is often more akin to mopping up the floor while the faucet runs and the sink continues to overflow. We need to turn off the faucet.

That is why I prepared a home study course on diabesity for my patients and consumers based on 20 years of practice treating thousands of patients with diabesity. I hope you receive this letter in the spirit of inquiry and cooperation that I believe is needed for patients and physicians to find the best possible treatment for each person.

Your patient has read my report and home study course on diabesity—the continuum of metabolic syndrome and diabetes. My approach is based on the science of functional medicine, a systems biology approach to dealing with chronic illness that attempts to assess the underlying network of causes and factors that promote disease as well as incorporating strategies to optimize and enhance normal gene expression, biochemistry, and physiology.

The key things that I have identified from my practice and research include the following:

- 1. Metabolic syndrome and diabetes are best approached through comprehensive lifestyle and environmental change. The data supports this approach as more effective than medication or surgery.
- 2. Specific tests can help in the early assessment and diagnosis of metabolic syndrome, as well as assess the severity of metabolic syndrome and diabetes. Some of these tests may be familiar, while others are not. Lipid particle size, for example, is a critical part of assessment of the dyslipidemia associated with metabolic syndrome.
- 3. Monitoring a basic panel of tests is necessary, as well as some additional tests that assess the secondary phenomena associated with insulin resistance such as fatty liver, inflammation, thyroid dysfunction, androgen deficiency in men, and androgen excess and PCOS in women.
- 4. Treatment of metabolic syndrome and diabetes with a low glycemic load, high-fiber, nutrient-dense, plant-based diet; regular exercise; stress management tools; reduction of exposure to environmental toxins; and selective research-based nutritional supplementation such as omega-3 fatty acids can more effectively treat the disease than medication and often even reverse the pathology. This can reduce overall medical expenses, care, and morbidity and mortality.

My home study course entitled *The Blood Sugar Solution* provides patients with all the tools they need for self-care to implement the lifestyle changes needed to address this epidemic. However, I have encouraged them to partner with their physician for testing, monitoring of

their care, and adjustment of medications as needed as they become healthier. As a practicing physician, I know that most of us neither have the time, nor often the training to teach our patients about sustainable behavioral and lifestyle change. I work closely with a nutritionist, but most do not have that luxury. This home study course, I hope, can be an adjunct to your practice and allow you to provide your patients a comprehensive approach to change that addresses the causes of their metabolic syndrome and diabetes.

With that in mind I have provided here what I hope are some useful tools, references and resources:

- 1. A list of the basic tests and interpretation that I use in my practice to monitor patients with metabolic syndrome and diabetes. I hope you will find them helpful and useful in monitoring your patients.
- 2. An editorial I published in 2006 entitled *Diabetes: Asking the Right Questions* explaining some of the science behind this approach.
- 3. An extensive list of references documenting everything I have said or recommended in this letter and the home study course.

Thank you for taking the time to review this letter. I encourage you to consider this perspective in your practice. I would like to offer this home study course as a support for your patient care.

If you would like further information on the field of Functional medicine and more detail about how to address our burden of chronic disease using a systems approach, I encourage you to read the *Textbook of Functional Medicine*. For further resources and training including the Certification Program in Functional Medicine, please visit www.functionalmedicine.org.

Sincerely,

Mark Hyman, MD

Diabesity Testing for Health Professionals

To Diagnose Presence of Diabesity

• Insulin Response Test

Fasting, 1-hour, and 2-hour glucose and insulin levels after a 75-gram glucose load. It's like a glucose tolerance test but measures both glucose and insulin. Your blood sugar can be normal but your insulin can be sky high. Fasting insulin should be < 5 IU/dl and 1- and 2-hour levels less than 30 IU/dl. Fasting blood sugar should be < 90 mg/dl and 1- and 2-hour less than 120 mg/dl.

Demand this test.

It is the most important indicator of the presence and severity of diabesity, but it is rarely done in medical practices today. That is why diabesity is not diagnosed in 90 percent of the people who have it. An alternative is to measure just fasting and 30 minutes post-glucose- load glucose and insulin levels. If you have already been diagnosed with diabetes, you don't need to do the 2-hour glucose-load test.

Hemaglobin A1c

This test measures the average of the last six weeks of blood sugar. Abnormal is > 5.5% of total hemoglobin.

• NMR lipid profile

This test determines the particle size and number of LDL, HDL, and triglycerides. Small, dense particles are dangerous and an indicator of diabesity, even if your overall cholesterol is normal with or without medication. You should have fewer than 1,000 total LDL particles and fewer than 500 small LDL particles (the dense, dangerous type). This test is performed by LipoScience, but can be ordered through LabCorp, a laboratory testing company.

• Lipid panel

This panel shows total cholesterol (ideal < 180 mg/dl), LDL (ideal < 70 mg/dl), HDL cholesterol (ideal > 60 mg/dl), and triglycerides (ideal < 100 mg/dl). Triglyceride/HDL ratio. Abnormal is greater than 4. Total cholesterol /HDL ratio. Abnormal is greater than 3.

Additional Tests for Diabesity

To Assess Severity of Complications of Diabesity

- **High-sensitivity C-reactive protein** (abnormal > 1.0 mg/liter) to assess inflammation.
- **Fibrinogen** (abnormal > 350 mg/deciliter) to assess clotting risk and thick blood.
- Lipoprotein (a) (abnormal > 30 nmol/L) to assess treatable genetic cholesterol marker.
- Uric acid (abnormal > 7.0 mg/dl) to assess gout risk caused by diabesity.
- **Homocysteine** (abnormal > 8.0 micromoles/liter) a sensitive marker for folate deficiency.
- Ferritin (abnormal > 200 ng/ml) to assess inflammation and iron status.
- Liver function tests (elevated AST, ALT, GGT are abnormal) to assess fatty liver.
- Kidney function tests (BUN abnormal > 20 mg/dl, creatinine abnormal > 1.2 mg/dl)

 to assess kidney function.
- **Microalbumin** (abnormal > 20 mg/dl) to assess protein in urine, an early marker for damage to kidneys.
- **25 OH vitamin D** (abnormal <45-60 ng/dl) 50-80 ng/dl for vitamin D status.
- **Thyroid hormones** (abnormal TSH, free T3, free T4, TPO antibodies) to assess thyroid function.
- Sex hormones (male total and free testosterone; and female FSH, LH, DHEA-S, estradiol, progesterone, free testosterone, and sex hormone binding globulin) to assess sex hormones.

Optimal Blood Sugar Levels

- Fasting blood sugar should be less than 80 mg/dL
- Thirty-minute, one-hour and two-hour glucose should not rise above 110 mg/dL, some say 120 mg/dL

Optimal Insulin Levels

• Fasting insulin should be between 2 IU/dL and 5, anything greater than 10 IU/dL is significantly elevated.

• Thirty-minute and one-hour and two-hour should be less than 25 IU/dL to 30 IU/dL. Anything higher than 30 IU/dL indicates some degree of insulin resistance.

Optimal Cholesterol Levels

- Total cholesterol < 180 mg/dL
- LDL cholesterol < 70 mg/dL
- HDL cholesterol > 60 mg/dL
- Triglycerides < 100 mg/dL
- Total cholesterol/HDL ratio < 3.0
- Triglyceride to HDL ratio < 4

Optimal NMR Tests (Nuclear Magnetic Resonance Lipid Particle Size)

Available from LabCorp or LipoScience

- Total LDL particles < 1000 nmol/L
- Total small LDL particles < 500 nmol/L
- LDL size > 21 nm
- HDL size > 9 nm/L
- VLDL < 0.1 nm/L

Renal Function Optimal Levels

- Microalbumin: Less than 20 mg/dL
- BUN: Less than 20 mg/dL
- Creatinine: Less than 1.2 mg/dL

Hormonal Imbalances: Common in Diabesity

Thyroid Dysfunction

People with diabesity often have problems with thyroid function, and it is often

undiagnosed. I recommend checking TSH, free T3, free T4, thyroid peroxidase antibodies,

baseline test to assess thyroid function.

- Ultrasensitive TSH (ideal range is between 1 and 2): This is a measure of the pituitary hormone that controls the thyroid.
- Free T3 and free T4: These are a measure of the circulating thyroid hormones.
 - The normal level of free T4 is usually between 0.9 and 1.8 ng/dl.

- The level of free T3 that is normal is considered to be between 240 and 450 pg/ml, depending on the laboratory measurements. However, the reference ranges for laboratory tests are often based on "normal populations."
 (Remember "normal" means the average of population, not necessarily the ideal.)
- TPO (thyroid peroxidase) and antithyroglobulin antibodies: Autoimmune antibodies in the thyroid gland that interfere with its function. These should both be less than 20 IU/mL.

Optimal Levels of Sex Hormones

Men:

- Total testosterone: Greater than 500 nanograms/dL
- Free Testosterone Greater than 20 picograms/dL

Women

- Free testosterone: Less than 0.5 to 5.0 picograms/dL
- DHEA-S: <200 mg/dL
- LH/FSH ratio: < 3:1
- Estradiol (depends on age and time of cycle)
- Progesterone (depends on age and time of cycle)

DIABETES—ASKING THE RIGHT QUESTIONS

Mark A. Hyman, MD

Mark A. Hyman, MD, is the editor-in-chief of *Alternative Therapies in Health and Medicine.* (*Altern Ther Health Med.* 2006; 12(5):10-13.)

It ain't what you don't know that gets you into trouble. It's what you know for sure that just ain't so.

-Mark Twain

n science, as in life, we receive answers to only the questions we ask. How is this true in the explosive increase in diabetes worldwide? How might diabetes be a model for a new way to diagnosis and treat chronic complex illnesses? Unfortunately, we are married to definitions and risk factors and not exploring more fruitful lines of inquiry. We are mired in asking the wrong questions, much like the religious sages of the middle ages who wondered how many angels could dance on the head of a pin. What is the correct definition of diabetes or insulin resistance or metabolic syndrome or pre-diabetes? Should we be excited by the latest drug therapy or gene discovery in diabetes? What about CAM therapies? Should we be assessing old or new therapies as "green drugs" to control blood sugar or lipids? Are these useful questions or simply distractions from the more important question of how to deal with diabetes from a cultural, social, political, etiologic, and comprehensive systemic, biological perspective?

Does asking the wrong questions distract from the larger notion of discovering the causes of disturbances in the dynamic continuum of our metabolic equilibrium and their remediation? Does asking the wrong questions deflect from inquiry into the critical processes of restoring self-regulation to our complex biology? I would argue that the answer to these questions is yes.

Understanding that illness has purpose and that disease is generally rooted in the body's attempt to correct underlying imbalances or dysfunction, we can seek to not alter, block, or interfere with normal metabolic processes, but to learn how to enhance, facilitate, and promote normal function. Symptoms are clues to deeper molecular, metabolic, and psycho-spiritual problems. They are welcome signposts guiding us to the imbalances, dysfunction and causes of illness. Symptoms are not enemies to be silenced, but friends that can orient us in the maze of metabolic accommodations resulting from the collision of genes, environment, and lifestyle we call disease.

So how do we reorient ourselves to more effectively address

the biggest worldwide epidemic threatening our species, an epidemic that threatens our children and shortens our life expectancy for the first time in history?¹ One billion people worldwide are overweight; 300 million are obese. One in 3 children born today will have type 2 diabetes in their lifetime. The rates of diabetes are increasing exponentially, both in developed countries and in developing worlds. In 1985, an estimated 30 million people worldwide had diabetes. In 2000, 150 million were "afflicted." It is estimated that by 2025, 350 million will have diabetes.² The World Health Organization (WHO) estimates that 2.5% to 15% of annual health budgets are spent on diabetes-related illnesses.³ Despite advances in diagnosis and pharmacologic therapies, the crisis continues unabated.

Perhaps we are thinking about the problem in old ways, and we need to reorient from treating the disease of diabetes and focus on the underlying metabolic dysfunctions that arise from lifestyle choices and cultural habits that destine a pharmacological approach for failure. Treating a patient who does not exercise; eats a nutrient-poor diet that includes white flour, refined sugars, and trans fatty acids, and that is low in fiber, omega 3 fatty acids, and phytonutrients; and who does not sleep enough with the latest peroxisome proliferator-activated receptor (PPAR) agonist or statin can be likened to pushing an enormous boulder up a mountain.

The diabetic constellation of hypertension, dysglycemia, dyslipidemia, visceral obesity, inflammation, oxidative stress, mitochondrial dysfunction, and coagulopathy is the tip of a much larger iceberg.⁴ While we may have to temporarily lower elevations in blood pressure, lipids or glucose, this cannot be our long-term strategy. We can chip away at the tip of the iceberg or dive deep to find the proximal causes rooted in our way of living, eating, sleeping, and moving our bodies, in the way we have left the source of the natural conditions that sustain life. Our ancestors did not need scientists, nutritionists, the media, or diet books to tell us what to eat to sustain human life. Unfortunately, we now need these things because we are lost in the supermarket forest, unsure of what items to hunt and gather to nourish our bodies appropriately.

We study each symptom or manifestation of disease in isolation, sometimes seeking to combine treatments in a new "polypill"⁵ (statin, beta-blocker, ACE inhibitor, aspirin, folate) that can reduce the burden of disease. This approach fails to recognize that thousands of variables and dynamic alterations in disease come from a very few original causes—this principle is the foundation of biological or functional medicine. The "polymeal" (wild salmon, wine, dark chocolate, almonds, fruits, vegetables, and garlic) might be a more effective and sensible solution with greater benefit.⁶

The simplicity of this perspective is founded in 2 guiding clinical notions. First, find and remove or correct the obstructions to normal biological function (and they are few—genes, dietary inputs, toxins, infections, allergens, and stress). Second, provide the more natural conditions (necessarily unique to each individual) for proper biologic and psycho-spiritual functioning (they are also few—quality protein, fat, carbohydrates, vitamins, minerals, phytonutrients, conditionally essential nutrients, water, air, sleep, rhythm, love, community).⁷ The name or definition of disease and the treatment of disease become less important than correcting the internal milieu that gave rise to symptoms. We cannot escape the exigencies of being born into the animal world, dependent on nature and each other in order to thrive.

SIDETRACKED BY THE NAME

A recent pair of editorials in the American Journal of Clinical Nutrition argued the merits and limitations of the various definitions of metabolic syndrome, a precursor to diabetes, and a significant disease risk factor unto itself. Gerald Reaven, the physician who first coined the term "Syndrome X," later called "metabolic syndrome," believes that while this appellation is useful in research, the concept has no clinical utility.⁸ It distracts, he says, from the more important task of identifying and treating each risk factor separately and aggressively—control the blood pressure, the lipid profile, the inflammation, the coagulopathy, and the glucose metabolism—and applies equally to metabolic syndrome or diabetes.

The World Health Organization, the Adult Treatment Plan III (ATP III), and the International Diabetes Federation all have different definitions of metabolic syndrome, including with varying importance abnormal fasting or post glucose load glucose, highdensity lipoprotein (HDL) and triglyceride levels, blood pressure, and obesity or waist circumference. While this homogenization of definitions may have academic utility, it is not particularly helpful in working with the single patient in a clinical setting. The problem with names and labels is that they abort the thinking process. They abort thinking about the state of a person's individual constitution-their unique genetic constellation interacting with their nutritional, immune, endocrine, or overall metabolic state-what has been referred to as the biological terrain or internal milieu. That terrain might be a better starting part for clinical disease management than attempting to match a patient to an existing or new International Classification of Diseases (ICD-10) definition. Many patients will not fit into the box of diagnosis. Some may have normal lipids or glucose but severe hyperinsulinemia, or central obesity, but normal glucose metabolism. They also may have different precipitating causes from dietary indiscretions to inflammatory or toxic etiologies layered upon a sea of genetic variation.

Grundy, in an accompanying editorial, makes the argument for an understanding that recognizes the interaction of all aspects of the "syndrome" —dyslipidemia, dysglycemia, hypertension, visceral obesity, inflammation, and coagulopathy—as a unifying principle that can help in early pattern recognition of metabolic derangement. Grundy reminds us that, "Whereas single-disorder organizations and sub-specialties may find it difficult to embrace risk-factor clustering as a new prevention paradigm, its reality makes a move in this direction virtually inevitable."⁹ Perhaps treating the risk factors is less important than treating the patterns they form at their root.

Taken in isolation, any study-whether basic science or translational clinical research-provides a limited guide for clinical care. Yet when considered together, patterns, themes, principles, and guiding concepts emerge. The National Institutes of Health (NIH) New Roadmap initiative recognizes the importance of systems thinking, patterns, and networks of function in disease and health. And the NIH is supporting basic research in this area. Yet the gap between basic sciences, epidemiology, and clinical care is vast because our approach to chronic conditions like diabetes is focused on treating downstream effects, and not a comprehensive view of the causes and their remediation. If the disease is primarily a lifestyle, nutritional, and metabolic disorder, why do we seek new drugs or employ outdated dietary recommendations from organizations such as the American Diabetes Association, which ignores the reality that the content of food is equally important as the calories?

BEYOND THE NAME: SEARCHING FOR MEANING AND ORDER IN CHAOS

So what do we know about the causes of diabetes or metabolic syndrome? What do we know about the various factors that influence its expression? And what do we know about the ways to influence genes and metabolism that reorganizes the abnormal patterns of function that appear clinically—the hyperinsulinemia, dyslipidemia, inflammation, oxidative stress, mitochondrial dysfunction, coagulopathy, hypertension, and central obesity? Is there a way of thinking and treating the patient in the clinic that addresses all of these problems simultaneously without addressing any one of them individually or directly? The answer, I believe, is yes.

I propose that diabetes is a clinical model for a problem that is endemic to clinical medicine—treating the symptoms, not the cause—and that understanding how to improve the biological terrain; optimize nutrient status; improve gene expression through specific nutrients and phytonutrients; and regulate immunity and metabolism via lifestyle interventions such as diet, exercise, stress management, and adequate sleep collectively can have a much greater impact than any pharmacologic treatment.

What does the evidence indicate might play a role in the development of insulin resistance, metabolic syndrome, and type 2 diabetes? A key epidemiological study by Willett et al assessed the collective effects of an improved dietary pattern (low glycemic load, high cereal fiber,¹⁰ high polyunsaturated and monounsaturated¹¹ fatty acids, low trans fats); moderate to vigorous exercise 30 minutes per day; no current smoking; and the consumption of half an alcoholic beverage per day. It was esti-

mated that in the 84,941 women followed in the study, 91% of all diabetes could be prevented. $^{\rm 12}$

There are hundreds more genes that help us adapt to starvation than to excess calories. Learning to influence gene regulation and expression through dietary, lifestyle, and environmental influences on PPAR and nuclear factor kappa binding (NFkB) and other key receptors and transcription factors is critical.

Over 35% of our calories come from 2 engineered foods foreign to human genes and biology—the genetically novel epic monocultures of corn and soybeans that infuse nearly all industrial foods produced through commercial agriculture or food processing.¹³ These industrial foods have untoward effects on human physiology and metabolism. They alter and become our cellular structure. Eating whole foods, native in design and beneficial to gene expression and cellular functioning is more sensible (and scientifically sound), than forming our cells and tissues of recently developed material that is biologically questionable.

The information in food and the science of nutrigenomics¹⁴ is a more useful guiding paradigm in the treatment of disease than understanding food as simply a source of energy, with all calories being equal in their metabolic effects. The research points in quite a different direction.

The quality and source of fat, carbohydrate, and protein qualitatively and quantitatively influences all the biological systems involved in insulin resistance and type 2 diabetes. Plantbased whole-food dietary patterns can prevent or even reverse underlying pathologies and metabolic dysfunction.¹⁵ Dietary fatty acid composition also plays a critical role—eliminating trans and saturated fats and increasing omega 3 and monounsaturated fats improves all parameters of diabetes and metabolic syndrome—the hyperinsulinemia, dyslipidemia, inflammation, oxidative stress, mitochondrial dysfunction, coagulopathy, hypertension, and central obesity.¹⁶ Carbohydrate quality is equally important-low-glycemic-load and -index carbohydrates with a high fiber content have similar benefit.¹⁷ Adequate protein nutrition also plays a role in glucose metabolism and can improve skeletal muscle function and reduce post-prandial lipids, insulin, and glucose and grehlin secretions.¹⁸ Elimination of red meat from the diet improves microalbuminuria and fatty acid profiles in people with diabetes.¹⁹

Dietary fiber has salutary effects on weight, lipids, and glucose metabolism and is equivalent to sulfonylureas in lowering glycated hemoglobin.²⁰ Micronutrients such as chromium, zinc, magnesium, biotin, vitamin D, the B vitamins, and antioxidants also might play a key role in modulating the various components of metabolic syndrome.²¹ Conditionally essential nutrients such as lipoic acid, coenzyme Q10, and carnitine also play a physiologic role in metabolic syndrome.²² Phytonutrients such as the carotenoids,²³ almonds,²⁴ soy, and phytoestrogens²⁵ influence gene expression, favoring insulin sensitivity, and reduction in lipids, oxidative stress, inflammation and coagulopathy.

Other key lifestyle factors affect our metabolic equilibrium as well. Exercise alters skeletal muscle metabolism and improves glucose uptake, reduces low-density lipoprotein, raises HDL, lowers blood pressure, and reduces inflammation and oxidative stress.²⁶ Autonomic dysfunction with sympathetic over-activity exacerbates insulin resistance and lipid and glucose metabolism and promotes central obesity.²⁷ Therefore, techniques to enhance parasympathetic and reduce sympathetic activity, such as yoga or meditation, can have protective or even therapeutic benefit in metabolic syndrome and diabetes.

While these therapies may have a small or limited benefit when studied in isolation, when taken together to approximate the more natural conditions, foods, and activities with which we evolved, they can dramatically help prevent and treat the sentinel disease that is a central cause of the accelerating epidemic of degenerative diseases including cardiovascular, neurodegenerative, and neoplastic conditions that afflict our aging population and our children. Disease is not a natural consequence of life to be accepted, but a reflection of the loss of the natural and evolutionary conditions necessary for self-regulation and healing. It is the body's best attempt to restore balance given a difficult set of circumstances. Learning to restore our capacity for self-regulation and metabolic equilibrium is the hope of the next generation of medical scientists and practitioners.

REFERENCES

- Olshansky SJ, Passaro DJ, Hershow RC, et al. A potential decline in life expectancy in the United States in the 21st century. *N Engl J Med.* 2005;352(11):1138-1145.
- 2. International Diabetes Federation. Diabetes prevention. Available at: http://www.idf.org/home/index.cfm?node=264. Accessed July 20, 2006.
- International Diabetes Federation. The costs of diabetes. Available at: http://www.idf.org/home/index.cfm?unode=3B9691D3-C026-2FD3-87B7FA0B63432BA3. Accessed July 26, 2006.
- Beckman JA, Creager MA, Libby P. Diabetes and atherosclerosis: epidemiology, pathophysiology, and management. *JAMA*. 2002;287(19):2570-2581. Review.
- Wald NJ, Law MR. A strategy to reduce cardiovascular disease by more than 80%. BMJ. 2003;326(7404):1419.
- Franco OH, Bonneux L, de Laet C, Peeters A, Steyerberg EW, Mackenbach JP.The Polymeal: a more natural, safer, and probably tastier (than the Polypill) strategy to reduce cardiovascular disease by more than 75%. *BMJ*. 2004;329(7480):1447-1450. Review.
- Hyman M, Baker SM, Jones DS. Functional medicine and biochemical individuality: a paradigm shift in medicine. In: Jones DS, Quinn S, eds. *Textbook of Functional Medicine*, Gig Harbor, Wash: Institute for Functional Medicine; 2006:55-63.
- Reaven GM.The metabolic syndrome: is this diagnosis necessary? Am J Clin Nutr. 2006;83(6):1237-1247.
- 9. Grundy SM. Does a diagnosis of metabolic syndrome have value in clinical practice? *Am J Clin Nutr.* 2006;83(6):1248-1251.
- Montonen J, Knekt P, Jarvinen R, Aromaa A, Reunanen A. Whole-grain and fiber intake and the incidence of type 2 diabetes. *Am J Clin Nutr.* 2003;77(3):622-629.
- Garg A. High-monounsaturated-fat diets for patients with diabetes mellitus: a metaanalysis. Am J Clin Nutr. 1998;67(3):577S-582S.
- Hu FB, Manson JE, Stampfer MJ, et al. Diet, lifestyle, and the risk of type 2 diabetes mellitus in women. N Engl J Med. 2001;(11):790-797.
- 13. Pollan M. The Omnivore's Dilemma. New York: Penguin Press; 2006.
- Phillips C, Lopez-Miranda J, Perez-Jimenez F, McManus R, Roche HM. Genetic and nutrient determinants of the metabolic syndrome. *Curr Opin Cardiol*. 2006;21(3):185-193.
- Jenkins DJ, Kendall CW, Marchie A, et al. Type 2 diabetes and the vegetarian diet. Am J Clin Nutr. 2003;78(3):610S-616S. Review.
- Salmeron J, Hu FB, Manson JE, et al. Dietary fat intake and risk of type 2 diabetes in women. Am J Clin Nutr. 2001;73(6):1019-1026.
- Gross LS, Li L, Ford ES, Liu S. Increased consumption of refined carbohydrates and the epidemic of type 2 diabetes in the United States: an ecologic assessment. *Am J Clin Nutr.* 2004;79(5):774-779.
- Gannon MC, Nuttall FQ, Saeed A, Jordan K, Hoover H. An increase in dietary protein improves the blood glucose response in persons with type 2 diabetes. *Am J Clin Nutr.* 2003;78(4):734-741.
- de Mello VD, Zelmanovitz T, Perassolo MS, Azevedo MJ, Gross JL. Withdrawal of red meat from the usual diet reduces albuminuria and improves serum fatty acid profile in type 2 diabetes patients with macroalbuminuria. *Am J Clin Nutr.* 2006;83(5):1032-1038.
- Chandalia M, Garg A, Lutjohann D, von Bergmann K, Grundy SM, Brinkley LJ. Beneficial effects of high dietary fiber intake in patients with type 2 diabetes mellitus. N Engl J Med. 2000;342(19):1392-1398.
- 21. Triggiani V, Resta F, Guastamacchia E, et al. Role of antioxidants, essential fatty acids,

carnitine, vitamins, phytochemicals and trace elements in the treatment of diabetes mellitus and its chronic complications. *Endocr Metab Immune Disord Drug Targets*. 2006;6(1):77-93. Review.

- 22. Henriksen EJ. Exercise training and the antioxidant alpha-lipoic acid in the treatment of insulin resistance and type 2 diabetes. *Free Radic Biol Med.* 2006;40(1):3-12. Review.
- 23. Coyne T, Ibiebele TI, Baade PD, et al. Diabetes mellitus and serum carotenoids: findings of a population-based study in Queensland, Australia. *Am J Clin Nutr.* 2005;82(3):685-693.
- 24. Jiang R, Manson JE, Stampfer MJ, Liu S, Willett WC, Hu FB. Nut and peanut butter consumption and risk of type 2 diabetes in women. *JAMA*. 2002;288(20):2554-2560.
- Bhathena SJ, Velasquez MT. Beneficial role of dietary phytoestrogens in obesity and diabetes. Am J Clin Nutr. 2002 Dec;76(6):1191-1201. Review.
- 26. Klein S, Sheard NF, Pi-Sunyer X, et al. Weight management through lifestyle modification for the prevention and management of type 2 diabetes: rationale and strategies. A statement of the American Diabetes Association, the North American Association for the Study of Obesity, and the American Society for Clinical Nutrition. *Am J Clin Nutr.* 2004;80(2):257-263. Review.
- 27. Rosmond R, Dallman MF, Bjorntorp P. Stress-related cortisol secretion in men: relationships with abdominal obesity and endocrine, metabolic and hemodynamic abnormalities. *J Clin Endocrinol Metab.* 1998;83(6):1853-1859.

Medical References from *The Blood Sugar Solution*

Preface

The Textbook of Functional Medicine, Institute of Functional Medicine, 2005

Introduction

1. Garber AJ, et al. Diagnosis and management of prediabetes in the continuum of hyperglycemia: when do the risks of diabetes begin? A consensus statement from the American College of Endocrinology and the American Association of Clinical Endocrinologists. *Endocr Pract.* 2008 Oct;14(7):933–46.

2. DECODE Study Group, European Diabetes Epidemiology Group. Is the current definition for diabetes relevant to mortality risk from all causes and cardiovascular and noncardiovascular diseases? *Diabetes Care*. 2003 Mar;26(3):688–96.

3. Lin SX, PiSunyer EX Prevalence of the metabolic syndrome among US middle-aged and older adults with and without diabetes — a preliminary analysis of the NHANES 1999–2002 data. *Ethn Dis*. 2007 Winter;17(1):35–39.

4. http://www.who.int/mediacentre/news/releases/2007/pr61/en/index.html.

5. Chan JC, et al. Diabetes in Asia: epidemiology, risk factors, and pathophysiology. *JAMA*. 2009 May 27;301(20):2129–40.

6. http://apps.nccd.cdc.gov/DDTSTRS/FactSheet.aspx (National Diabetes Fact Sheet 2007).

7. http://www.cdc.gov/diabetes/statistics/cvd/fig5.htm.

8. Lakka HM, et al. The metabolic syndrome and total and cardiovascular disease mortality in middle-aged men. *JAMA*. 2002 Dec 4;288(21):2709–16.

9. Ott A, et al. Diabetes mellitus and the risk of dementia: The Rotterdam Study. *Neurology*. 1999 Dec 10;53(9):1937–42.

10. Key T, Reeves GK, Spencer EA. Symposium 1: Overnutrition: consequences and solutions for obesity and cancer risk. *Proc NutrSoc*. 2009 Dec 3:1–5.

11. Targher G, Day CP, Bonora E. Risk of cardiovascular disease in patients with nonalcoholic fatty liver disease. *N Engl J Med.* 2010 Sep 30;363(14):1341–50.

12. Pan A, et al. Bidirectional association between depression and type 2 diabetes mellitus in women. *Arch Intern Med*. 2010 Nov 22;170(21):1884–91.

13. Emerging Risk Factors Collaboration et al. Diabetes mellitus, fasting glucose, and risk of cause-specific death. *N Engl J Med*. 2011 Mar 3;364(9):829–41.

14. Huang ES, Basu A, O'Grady M, Capretta JC. Projecting the future: diabetes population size and related costs for the U.S. *Diabetes Care*. 2009 Dec;32(12): 2225–29.

15. Seligman HK, Schillinger D. Hunger and socioeconomic disparities in chronic disease. *N Engl J Med*. 2010 Jul 1;363(1):6–9.

16. Yach D, Hawkes C, Gould CL, Hofman KJ. The global burden of chronic diseases: overcoming impediments to prevention and control. *JAMA*. 2004 Jun 2; 291(21):2616–22.

17. Action to Control Cardiovascular Risk in Diabetes Study Group, Gerstein HC, et al. Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med*. 2008 Jun 12;358(24):2545–59.

18. Chen L, et al. Reduction in consumption of sugar- sweetened beverages is associated with weight loss: the PREMIER trial. *Am J Clin Nutr*. 2009 May;89(5):1299–306.

19. Bhashyam S, et al. Aging is associated with myocardial insulin resistance and mitochondrial dysfunction. *Am J Physiol Heart Circ Physiol*. 2007 Nov;293(5):H3063–71.

20. Ryan AS. Insulin resistance with aging: effects of diet and exercise. *Sports Med.* 2000 Nov;30(5):327–46.

21. Gaziano JM, et al. Fasting triglycerides, high- density lipoprotein, and risk of myocardial infarction. *Circulation*. 1997 Oct 21;96(8):2520–25.

22. McCarthy MI. Genomics, type 2 diabetes, and obesity. *N Engl JMed*. 2010 Dec 9;363(24):2339–50.

23. Rappaport SM. Implications of the exposome for exposure science. *J Expo Sci Environ Epidemiol*. 2011 Jan;21(1):5-9.

24. Lichtenstein P, et al. Environmental and heritable factors in the causation of cancer— analyses of cohorts of twins from Sweden, Denmark, and Finland. *N Engl JMed.* 2000 Jul 13;343(2):78–85.

25. Olshansky SJ, et al. A potential decline in life expectancy in the United States in the 21st century. *N Engl J Med*. 2005 Mar 17;352(11):1138–45.

26. Bibbins-Domingo K, et al. Adolescent overweight and future adult coronary heart disease. *N Engl JMed.* 2007 Dec 6;357(23):2371–79.

27. Diabetes Prevention Program Research Group, Knowler WC, et al. 10-year follow-up of diabetes incidence and weight loss in the Diabetes Prevention Program Outcomes Study. *Lancet*. 2009 Nov 14;374(9702):1677–86.

28. Lim EL, et al. Reversal of type 2 diabetes: normalisation of beta cell function in association with decreased pancreas and liver triacylglycerol. *Diabetologia*. 2011 Oct;54(10): 2506–14.

29. Henry B, Kalynovskyi S. Reversing diabetes and obesity naturally: a NEWSTART lifestyle program. *Diabetes Educ*. 2004 Jan- Feb; 30(1):48–50, 55–56, 58–59.

30. Jessani S, et al. Should oral glucose tolerance testing be mandatory following acute myocardial infarction? *Int J Clin Pract*. 2007 Apr;61(4):680–83.

31. Khaw KT, et al. Association of hemoglobin A1c with cardiovascular disease acute mortality in adults: the European prospective investigation into cancer in Norfolk. *Ann Intern Med.* 2004 Sep 21;141(6):413–20.

32. Yaffe K, et al. The metabolic syndrome, inflammation, and risk of cognitive decline. *JAMA*. 2004 Nov 10;292(18):2237–42.

33. de la Monte SM, Wands JR. Alzheimer's disease is type 3 diabetes - evidence reviewed. *J Diabetes Sci Technol*. 2008 Nov; 2(6):1101–13.

34. Stein JL, Jack CR Jr, Weiner MW, Toga AW, Thompson PM; Cardiovascular Health Study; ADNI. Obesity is linked with lower brain volume in 700 AD and MCI patients. *Neurobiol Aging*. 2010 Aug;31(8):1326–39.

35. http://www.acpm.org/Lifestyle Medicine.htm.

36. Haffner SM, et al. Mortality from coronary heart disease in subjects with type 2 diabetes and in non-diabetic subjects with and without prior myocardial infarction. *N Engl J Med.* 1998;339:229–34.

37. The NAVIGATOR Study Group. Effect of nateglinide on the incidence of diabetes and cardiovascular events. *N Engl J Med.* 2010. Apr 22;362(16):1463–76.

38. The NAVIGATOR Study Group. Effect of valsartan on the incidenceof diabetes and cardiovascular events. *N Engl J Med*. 2010. Apr 22;362(16):1477–90.

39. The ACCORD Study Group. Effects of combination lipid therapy in type 2 diabetes mellitus. *N Engl J Med.* 2010. Apr 29;362 (17):1563–74.

40. Taylor F, et al. Statins for the primary prevention of cardiovascular disease. *Cochrane Database Syst Rev.* 2011 Jan 19:CD004816.

41. Abramson J, Wright JM. Are lipid-lowering guidelines evidence-based? *Lancet*. 2007 Jan 20;369(9557):168–89.

42. Sirvent P, Mercier J, Lacampagne A. New insights into mechanisms of statin-associated myotoxicity. *Curr Opin Pharmacol.* 2008 Jun; 8(3):333–38.

43. Kuncl RW. Agents and mechanisms of toxic myopathy. *Curr Opin Neurol*. 2009 Oct;22(5):506–15. PubMed PMID: 19680127.

44. Tsivgoulis G, et al. Presymptomatic Neuromuscular Disorders Disclosed Following Statin Treatment. *Arch Intern Med.* 2006;166:1519–24.

45. Preiss D, et al. Risk of incident diabetes with intensive- dose compared with moderate- dose statin therapy: a meta- analysis. *JAMA*. 2011 Jun 22;305(24): 2556–64.

46. The BARI 2D Study Group. A randomized trial of therapies for type 2 diabetes and coronary artery disease. *N Engl J Med*. 2009 Jun 11;360:2503.

47. Newman MF, et al. Neurological Outcome Research Group and the Cardiothoracic Anesthesiology Research Endeavors Investigators. Longitudinal assessment of neurocognitive function after coronary- artery bypass surgery. *N Engl J Med*. 2001 Feb 8;344(6): 395–402.

48. Saliba J, Wattacheril J, Abumrad NN. Endocrine and metabolic response to gastric bypass. *Curr Opin Clin Nutr Metab Care*. 2009 Sep;12(5):515–21.

49. Sturm W, et al. Effect of bariatric surgery on both functional and structural measures of premature atherosclerosis. *Eur Heart J.* 2009 Aug;30(16):2038–43.

50. Gearhardt AN, Corbin WR, Brownell KD. Preliminary validation of the Yale Food Addiction Scale. *Appetite.* 2009;52(2): 430–36.

51. Gearhardt A, et al. Food addiction, an examination of the diagnostic criteria for dependence. *J Addict Med.* 2009;3:1–7.

52. Colantuoni C, Schwenker J, McCarthy P, et al. Excessive sugar intake alters binding to dopamine and mu-opioid receptors in the brain. *Neuroreport*. 2001;12(16): 3549–52.

53. Volkow, ND, Wang, GJ, Fowler, JS, et al. "Nonhedonic" food motivation in humans involves dopamine in the dorsal striatum and methylphenidate amplifies this effect. *Synapse.* 2002;44(3): 175–80.

54. Malik VS, Schulze MB, Hu FB. Intake of sugar-sweetened beverages and weight gain: a systematic review. *Am J Clin Nutr.* 2006 Aug;84(2):274–88.

55. Brownell KD, et al. The public health and economic benefits of taxing sugar-sweetened beverages. *N Engl J Med*. 2009 Oct 15; 361(16):1599–605. Epub 2009 Sep 16.

56. Wang YC, et al. Impact of change in sweetened caloric beverage consumption on energy intake among children and adolescents. *Arch Pediatr Adolesc Med*. 2009 Apr;163(4):336–43.

57. Ludwig DS, Peterson KE, Gortmaker SL. Relation between consumption of sugar- sweetened drinks and childhood obesity: a prospective, observational analysis. *Lancet*. 2001;357:505–8.

58. Ellenbogen SJ, et al. Effects of decreasing sugar- sweetened beverage consumption on body weight in adolescents: a randomized, controlled pilot study. *Pediatrics*. 2006;117:673–80.

59. Schulze MB, et al. Sugar- sweetened beverages, weight gain, and incidence of type 2 diabetes in young and middle- aged women. *JAMA*. 2004;292(8):927–34.

60. Palmer JR, et al. Sugar sweetened beverages and incidence of type 2 diabetes mellitus in African American women. *Arch Intern Med.* 2008;168(14):1487–92.

61. Fung TT, et al. Sweetened beverage consumption and risk of coronary heart disease in women. *Am J Clin Nutr.* 2009;89(4):1037–42.

62. Malik VS, Schulze MB, Hu FB. Intake of sugar-sweetened beverages and weight gain: a systematic review. *Am J Clin Nutr*. 2006;84(2):274–88.

63. Wang YC, et al. Impact of change in sweetened caloric beverage consumption on energy intake among children and adolescents. *Arch Pediatr Adolesc Med.* 2009; 163(4):336–343.

64. Dennis EA, et al. Water consumption increases weight loss during a hypocaloric diet intervention in middle- aged and older adults. *Obesity*. 2010 Feb;18(2):300–7.

65. Forshee RA, Anderson PA, Storey ML. Sugar-sweetened beverages and body mass index in children and adolescents: A metaanalysis. *Am J Clin Nutr.* 2008:87:1662–71.

66. Lesser LI, et al. Relationship between funding source and conclusion among nutrition- related scientific articles. *PLoS Med.* 2007 Jan;4(1):e5.

67. http://consumerfreedom.com/about.cfm.

68. Swithers SE, Davidson TL. A role for sweet taste: calorie predictive relations in energy regulation by rats. *Behav Neurosci*. 2008; 122(1):161–73.

69. Lenoir M, et al. Intense sweetness surpasses cocaine reward. *PLoS One*. 2007;2(1):e698.

70. Ludwig DS. Artificially sweetened beverages: cause for concern. *JAMA*. 2009 Dec 9;302(22): 2477–78.

71. <u>http://www.theatlant.ic.com/life/archive/2011/04/new-federal-guidelines-regulate-junk-food-</u>ads-for-kids/238053/

72. Nestle M. Food marketing andchildhood obesity— a matter of policy. *N Engl J Med*. 2006 Jun 15;354(24):2527–29.

73. http://www.cspinet.org/new/200709171.html

74. Kahneman DA. Perspective on judgment and choice: mapping bounded rationality. *Am Psychol.* 2003 Sep;58(9):697–720.

75. Barry CL, et al. Obesity metaphors: how beliefs about the causes of obesity affect support for public policy. *Milbank Q*. 2009 Mar;87(1):7–47.

76. Snyderman R, Williams RS. Prospective medicine: the next health care transformation. *AcadMed*. 2003 Nov;78(11):1079–80.

77. Nelson RA, Bremer AA. Insulin resistance and metabolic syndrome in the pediatric population. *Metab Syndr Relat Disord*. 2010 Feb;8(1):1–14.

78. Silverstein JH, Rosenbloom AL. Type 2 diabetes in children. *CurrDiab Rep*. 2001 Aug;1(1):19–27.

79. The Textbook of Functional Medicine. Institute of Functional Medicine, 2005.

80. Choi HK, Willett W, Curhan G. Fructose-rich beverages and risk of gout in women. *JAMA*. 2010 Nov 24;304(20):2270–78.

81. Gillis L, Gillis A. Nutrient inadequacy in obese and non-obese youth. *Can J Diet Pract Res.* 2005 Winter;66(4):237–42.

82. Cordain L, et al. Origin and evolution of the Western diet: health implications for the 21st century. *Am J Clin Nutr*. 2005;8(2):341–54.

83. United States Department of Agriculture. Agriculture Factbook Chapter 2: Profiling Food Consumption in America. 2001. Accessed online (http://www.usda.gov/factbook/chapter2.pdf).

84. Dufault R, et al. Mercury from chlor- alkali plants: measured concentrations in food product sugar. *Environ Health*. 2009 Jan 26;8:2.

85. Bray GA, Nielsen SJ, Popkin BM. Consumption of high-fructose corn syrup in beverages may play a role in the epidemic of obesity. *Am J Clin Nutr.* 2004 Apr;79(4):537–43.

86. Eaton SB, Konner M. Paleolithic nutrition: a consideration of its nature and current implications. *N Engl J Med*. 1985 Jan 31;312(5): 283–89.

87. Robson AA. Preventing diet induced disease: bioavailable nutrient-rich, low-energy-Dense diets. *Nutr Health*. 2009;20(2): 135–66.

88. Chandalia M, et al. Beneficial effects of high dietary fiber intake in patients with type 2 diabetes mellitus. *N Engl J Med*. 2000 May 11;342(19):1392–98.

89. Reis JP, et al. Vitamin D status and cardiometabolic risk factors in the United States adolescent population. *Pediatrics*. 2009 Sep; 124(3):e371–79.

90. A scientific review: the role of chromium in insulin resistance. *Diabetes Educ*. 2004;Suppl:2–14.

91. Lau FC, Bagchi M, Sen CK, Bagchi D. Nutrigenomic basis of beneficial effects of chromium(III) on obesity and diabetes. *Mol Cell Biochem*. 2008 Oct;317(1–2):1–10. *Epub.* 2008 Jul 18. Review.

92. Chaudhary DP, Sharma R, Bansal DD. Implications of magnesium deficiency in type 2 diabetes: A review. *Biol Trace Elem Res.* 2010 May;134(2):119–29.

93. Masood N, et al. Serum zinc and magnesium in type-2 diabetic patients. *J Coll Physicians Surg Pak*. 2009 Aug;19(8):483–86.

94. Albarracin CA, et al. Chromium picolinate and biotin combination improves glucose metabolism in treated, uncontrolled overweight to obese patients with type 2 diabetes. *Diabetes Metab Res Rev.* 2008 Jan- Feb; 24(1):41–51.

95. Flachs P, et al. Cellular and molecular effects of n-3 polyunsaturated fatty acids on adipose tissue biology and metabolism. *Clin Sci.* 2009 Jan;116(1):1-16.

96. Shay KP, et al. Alpha-lipoic acid as a dietary supplement: molecular mechanisms and therapeutic potential. *Biochim Biophys Acta*. 2009 Oct;1790(10):1149–60.

97. Ornish D, et al. Changes in prostate gene expression in men undergoing an intensive nutrition and lifestyle intervention. *Proc Natl Acad Sci U S A*. 2008 Jun 17;105(24):8369–74.

98. Kallio P, et al. Dietary carbohydrate modification induces alterations in gene expression in abdominal subcutaneous adipose tissue in persons with the metabolic syndrome: the FUNGENUT Study. *Am J Clin Nutr.* 2007 May;85(5):1417–27.

99. Salsberg SL, Ludwig DS. Putting your genes on a diet: the molecular effects of carbohydrate. *Am J Clin Nutr.* 2007 May;85(5):1169–70.

100. Giugliano D, Esposito K. Mediterranean diet and metabolic diseases. *Curr Opin Lipidol*. 2008 Feb;19(1):63–68.

101. Reis JP, et al. Vitamin D status and cardiometabolic risk factors in the United States adolescent population. *Pediatrics*. 2009 Sep; 124(3):e371–79.

102. Chaudhary DP, Sharma R, Bansal DD. Implications of magnesium deficiency in type 2 diabetes: A review. *Biol Trace Elem Res.* 2010 May;134(2):119–29.

103. Poh Z, Goh KP. Current update on the use of alpha lipoic acid in the management of type 2 diabetes mellitus. *Endocr Metab Immune Disord Drug Targets*. 2009 Dec; 9(4): 392–98.

104. Kligler B, Lynch D. An integrative approach to the management of type 2 diabetes mellitus. *Altern Ther Health Med.* 2003 Nov-Dec; 9(6):24–32; quiz 33.

105. Kelly GS. Insulin resistance: lifestyle and nutritional interventions. *Altern Med Rev*. 2000 Apr;5(2):109–32.

106. Kreisberg J. Learning from organic agriculture. *Explore.* 2006 Sep-Oct; 2(5):450–52.

107. Fairfield KM, Fletcher RH. Vitamins for chronic disease prevention in adults: scientific review. *JAMA*. 2002 Jun 19;287(23): 3116–26.

108. Maratou E, et al. Studies of insulin resistance in patients with clinical and subclinical hypothyroidism. *Eur J Endocrinol*. 2009 May;160(5):785–90.

109. Ayturk S, et al. Metabolic syndrome and its components are associated with increased thyroid volume and nodule prevalence in a mild-to-moderate iodine-deficient area. *Eur J Endocrinol*. 2009 Oct;161(4):599–605.

110. Golden SH. A review of the evidence for a neuroendocrine link between stress, depression and diabetes mellitus. *Curr Diabetes Rev.* 2007 Nov;3(4):252–59.

111. Van Cauter E, et al. Impact of sleep and sleep loss on neuroendocrine and metabolic function. *Horm Res.* 2007;67 Suppl 1:2–9.

112. Garruti G, et al. Adipose tissue, metabolic syndrome and polycystic ovary syndrome: from pathophysiology to treatment. *Reprod Biomed Online*. 2009 Oct; 19(4):552–63.

113. Chavarro JE, et al. Diet and lifestyle in the prevention of ovulatory disorder infertility. *Obstet Gynecol.* 2007 Nov;110(5):1050–58.

114. Chavarro JE, et al. Use of multivitamins, intake of B vitamins, and risk of ovulatory infertility. *Fertil Steril*. 2008 Mar;89(3):668–76.

115. Rhodes ET, et al. Effects of a low-glycemic load diet in overweight and obese pregnant women: a pilot randomized controlled trial. *Am J Clin Nutr.* 2010 Dec;92(6): 1306–15.

116. Zitzmann M. Testosterone deficiency, insulin resistance and the metabolic syndrome. *Nat Rev Endocrinol*. 2009 Dec;5(12):673–81.

117. Deng Y, Scherer PE. Adipokines as novel biomarkers and regulators of the metabolic syndrome. *Ann NY Acad Sci.* 2010 Nov;1212(1):E1–E19.

118. Sedghizadeh PP, et al. Celiac disease and recurrent aphthous stomatitis: a report and review of the literature. *Oral Surg, Oral Med, Oral Pathol, Oral Radiol, and Endod*. 2002 Oct;94(4):474–78.

119. Freeman MP, et al. Omega-3 fatty acids: evidence basis for treatment and future research in psychiatry. *J Clin Psychiatry*. 2006 Dec;67(12):1954–67.

120. Vasquez, A. The clinical importance of vitamin D (cholecalciferol): a paradigm shift with implications for all healthcare providers, *Altern Ther Health Med.* 2004 Sep- Oct; 10(5):28-36.

121. Holick, M. Vitamin D: importance in the prevention of cancers, type 1 diabetes, heart disease and osteoporosis. *Am J Clin Nutr.* 2004;79:362–71.

122. Wilkins CH, et al. Vitamin D deficiency is associated with low mood and worse cognitive performance in older adults. *Am J Geriatr Psychiatry*. 2006 Dec;14(12): 1032–40.

123. Mischoulon D, Raab MF. The role of folate in depression and dementia. *J Clin Psychiatry*. 2007; 68 Suppl 10:28–33.

124. Penninx BW, et al. Vitamin B(12) deficiency and depression in physically disabled older women: epidemiologic evidence from the Women's Health and Aging Study. *Am J Psychiatry*. 2000 May; 157(5):715–21.

125. Almeida C, et al. Subclinical hypothyroidism: psychiatric disorders and symptoms. *Rev Bras Psiquiatr*. 2007 Jun;29(2):157–59.

126. Smith RN, et al. A low-glycemic-load diet improves symptoms in acne vulgaris patients: a randomized controlled trial. *Am J Clin Nutr*. 2007 Jul;86(1):107–15.

127. Koponen H, et al. Metabolic syndrome predisposes to depressive symptoms: a population-Based 7-year follow-up study. *J Clin Psychiatry.* 2008 Feb;69(2):178–82.

128. Ludvigsson JF, et al. Coeliac disease and risk of mood disorders- a general population-Based cohort study. *J Affect Disord.* 2007 Apr; 99(1–3): 117–26. Epub 2006 Oct 6.

129. Ch'ng CL, Jones MK, Kingham JG. Celiac disease and autoimmune thyroid disease. *Clin Med Res.* 2007 Oct;5(3):184–92.

130. Wilders- Truschnig M, et al. IgG antibodies against food antigens are correlated with inflammation and intima media thickness in obese juveniles. *Exp Clin Endocrinol Diabetes.* 2008 Apr;116(4): 241–45.

131. Pradhan AD, et al. C-reactive protein, interleukin 6, and risk of developing type 2 diabetes mellitus. *JAMA*. 2001 Jul 18;286(3):327–34.

132. Wilders-Truschnig M, et al. IgG antibodies against food antigens are correlated with inflammation and intima media thickness in obese juveniles. *Exp Clin Endocrinol Diabetes.* 2008 Apr;116(4):241–45.

133. Pelsser, et al. Effects of a restricted elimination diet on the behavior of children with attention-Deficit hyperactivity disorder (INCA study): a randomised controlled trial. *Lancet.* 2011;377:494– 503.

134. Cortese S, Morcillo Peñalver C. Comorbidity between ADHD and obesity: exploring shared mechanisms and clinical implications. *Postgrad Med.* 2010 Sep;122(5): 88–96.

135. Rubio-Tapia A, et al. Increased prevalence and mortality in undiagnosed celiac disease. *Gastroenterology.* 2009 Jul;137(1):88–93.

136. Ludvigsson JF, et al. Small-intestinal histopathology and mortality risk in celiac disease. *JAMA.* 2009 Sep 16;302(11): 1171–78.

137. Sapone A, et al. Divergence of gut permeability and mucosal immune gene expression in two gluten- associated conditions: celiac disease and gluten sensitivity. *BMC Med.* 2011 Mar 9;9:23.

138. Catassi C, Fasano A. Celiac disease diagnosis: simple rules are better than complicated algorithms. *Am J Med.* 2010 Aug; 123(8):691–93.

139. Atkinson RL. Viruses as an etiology of obesity. *Mayo Clin Proc.* 2007 Oct;82(10):1192–98.

140. Navas-Acien A, et al. Arsenic exposure and prevalence of type 2 diabetes in US adults. *JAMA.* 2008 Aug 20;300(7):814–22.

141. Jones OA, Maguire ML, Griffin JL. Environmental pollution and diabetes: a neglected association. *Lancet.* 2008 Jan 26;371(9609): 287–88.

142. Munhoz CD, et al. Stress-induced neuroinflammation: mechanisms and new pharmacological targets. *Braz J Med Biol Res.* 2008 Dec; 41(12):1037–46.

143. Smith JK, et al. Long-term exercise and atherogenic activity of blood mononuclear cells in persons at risk of developing ischemic heart disease. *JAMA.* 1999 May 12;281(18):1722–27.

144. Church TS, et al. Reduction of C-reactive protein levels through use of a multivitamin. *Am J Med.* 2003 Dec 15;115(9):702–7.

145. Larsen N, et al. Gut microbiota in human adults with type 2 diabetes differs from non-Diabetic adults. *PLoS One.* 2010 Feb 5; 5(2):e9085.

146. Tsai F, Coyle WJ. The microbiome and obesity: is obesity linked to our gut flora? *Curr Gastroenterol Rep.* 2009 Aug;11(4):307–13.

147. Bäckhed F, Ding H, Wang T, Hooper LV, Koh GY, Nagy A, Semenkovich CF, Gordon JI. The gut microbiota as an environmental factor that regulates fat storage. *Proc Natl Acad Sci U S A.* 2004 Nov 2;101(44):15718–23.

148. Cani PD, et al. Metabolic endotoxemia initiates obesity and insulin resistance. *Diabetes.* 2007 Jul;56(7):1761–72.

149. Jones OA, Maguire ML, Griffin JL. Environmental pollution and diabetes: a neglected association. *Lancet.* 2008 Jan 26;371(9609): 287–88.

150. <u>http://www.ewg.org/reports/bodyburden2/newsrelease.php</u>.

151. Lang IA, et al. Association of urinary bisphenol A concentration with medical disorders and laboratory abnormalities in adults. *JAMA.* 2008 Sep 17;300(11):1303–10.

152. Lee DH, et al. A strong dose-response relation between serum concentrations of persistent organic pollutants and diabetes: results from the National Health and Examination Survey 1999–2002. *Diabetes Care.* 2006 Jul;29(7):1638–44.

153. Navas-Acien A, Silbergeld EK, Pastor Barriuso R, Guallar E. Arsenic exposure and prevalence of type 2 diabetes in US adults. *JAMA*. 2008 Aug 20;300(7):814–22.

154. Fujiyoshi PT, Michalek JE, Matsumura F. Molecular epidemiologic evidence for diabetogenic effects of dioxin exposure in U.S. Air Force veterans of the Vietnam War. *Environ Health Perspect.* 2006 Nov;114(11):1677–83.

155. Chen JQ, Brown TR, Russo J. Regulation of energy metabolism pathways by estrogens and estrogenic chemicals and potential implications in obesity associated with increased exposure to endocrine disruptors. *Biochim Biophys Acta.* 2009 Jul;1793(7):1128–43.

156. Hyman M. Systems biology, toxins, obesity, and functional medicine. *Altern Ther Health Med.* 2007 Mar-Apr;13(2):S134-39.

157. Remillard RB, Bunce NJ. Linking dioxins to diabetes: epidemiology and biologic plausibility. *Environ Health Perspect.* 2002 Sep;110(9):853–38.

158. Griffin JL, Scott J, Nicholson JK. The influence of pharmacogenetics on fatty liver disease in the wistar and kyoto rats: a combined transcriptomic and metabonomic study. *J Proteome Res.* 2007 Jan;6(1):54–61.

159. Hampton T. Mitochondrial defects may play role in the metabolic syndrome. *JAMA.* 2004 Dec 15; 292(23):2823–24.

160. Petersen KF, et al. Impaired mitochondrial activity in the insulin-resistant offspring of patients with type 2 diabetes. *N Engl J Med.* 2004 Feb 12;350(7): 664–71.

161. Henriksen EJ, Diamond-Stanic MK, Marchionne EM. Oxidative stress and the etiology of insulin resistance and type 2 diabetes. *Free Radic Biol Med.* 2011 Sept 1;51(5):993–99.

162. Thomas DE, Elliott EJ, Naughton GA. Exercise for type 2 diabetes mellitus. *Cochrane Database Syst Rev.* 2006 Jul 19;3: CD002968.

163. Fontana L. The scientific basis of caloric restriction leading to longer life. *Curr Opin Gastroenterol.* 2009 Mar;25(2):144–50.

164. Valerio A, D'Antona G, Nisoli E. Branched-chain amino acids, mitochondrial biogenesis, and healthspan: an evolutionary perspective. *Aging.* 2011 May;3(5):464–78.

165. http://www.ultrawellness.com/blog/resveratrol

166. Holt RI, et al. Hertfordshire Cohort Study Group. The relationship between depression and diabetes mellitus: findings from the Hertfordshire Cohort Study. *Diabet Med.* 2009 Jun;26(6): 641–48.

167. Pan A, et al. Bidirectional association between depression and type 2 diabetes mellitus in women. *Arch Intern Med.* 2010 Nov 22;170(21):1884–91.

168. Dufault R, et al. Mercury from chlor-alkali plants: measured concentrations in food product sugar. *Environ Health.* 2009 Jan 26;8:2.

169. Boltri JM, et al. Diabetes prevention in a faith- based setting: results of translational research. *J Public Health Manag Pract.* 2008;14(1):29–32.

170. Knowler WC, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med.* 2002;346 (6):393–403.

171. Diabetes Prevention Program Research Group, et al. 10-year follow up of diabetes incidence and weight loss in the Diabetes Prevention Program Outcomes Study. *Lancet.* 2009 Nov 14; 374(9702):1677–86.

172. Ilanne-Parikka P, et al. Finnish Diabetes Prevention Study Group. Effect of lifestyle intervention on the occurrence of metabolic syndrome and its components in the Finnish Diabetes Prevention Study. *Diabetes Care.* 2008 Apr;31(4):805–7.

173. Look AHEAD Research Group, Wing RR. Long term effects of a lifestyle intervention on weight and cardiovascular risk factors in individuals with type 2 diabetes mellitus: four- year results of the Look AHEAD trial. *Arch Intern Med.* 2010 Sep 27;170(17): 1566–75.

174. United Health Center for Health Reform and Modernization, The United States of Diabetes. November 2010 (www.unitedhealthgroup.com/reform).

175. Schneider HJ, et al. The predictive value of different measures of obesity for incident cardiovascular events and mortality. *J Clin Endocrinol Metab.* 2010 Apr;95(4):1777–85.

176. Ebbeling CB, Leidig MM, Feldman HA, Lovesky MM, Ludwig DS. Effects of a low glycemic load vs low fat diet in obese young adults: a randomized trial. *JAMA.* 2007 May 16;297(19): 2092–102.

177. Larsen TM, et al. Diet, Obesity, and Genes (Diogenes) Project. Diets with high or low protein content and glycemic index for weight loss maintenance. *N Engl J Med.* 2010 Nov 25;363(22):2102–13.

178. Campbell TC. A study on diet, nutrition and disease in the People's Republic of China. Part I. *Bol Asoc Med P R.* 1990 Mar; 82(3):132–34.

179. Campbell TC. A study on diet, nutrition and disease in the People's Republic of China. Part II. *Bol Asoc Med P R.* 1990 Jul; 82(7):316–18.

180. Jiang R, et al. Nut and peanut butter consumption and risk of type 2 diabetes in women. *JAMA.* 2002 Nov 27;288(20):2554–60.

181. Fung TT, et al. Dietary patterns, meat intake, and the risk of type 2 diabetes in women. *Arch Intern Med.* 2004 Nov 8;164(20): 2235–40.

182. Arya F, et al. Differences in postprandial inflammatory responses to a 'modern' v. traditional meat meal: a preliminary study. *Br J Nutr.* 2010 Sep;104(5):724–28.

183. Luopajärvi K, et al. Enhanced levels of cow's milk antibodies in infancy in children who develop type 1 diabetes later in childhood. *Pediatr Diabetes.* 2008 Oct; 9(5):434–41.

184. Frisk G, et al. A unifying hypothesis on the development of type 1 diabetes and celiac disease: gluten consumption may be a shared causative factor. *Med Hypotheses.* 2008;70(6):1207–9.

185. de Kort S, Keszthelyi D, Masclee AA. Leaky gut and diabetes mellitus: what is the link? *Obes Rev.* 2011 Jun;12(6)449– 500.

186. Hoppe C, et al. High intakes of milk, but not meat, increase s-insulin and insulin resistance in 8-year old boys. *Eur J Clin Nutr.* 2005;59:393–98.

187. Liljeberg EH, Bjorck I. Milk as a supplement to mixed meals may elevate postprandial insulinanemia. *Eur J Clin Nutr.* 2001;55:994–99.

188. Kelly GS. Insulin resistance: lifestyle and nutritional interventions. *Altern Med Rev.* 2000 Apr;5(2):109–32.

189. Nikooyeh B, et al. Daily consumption of vitamin D - or vitamin D + calcium fortified Yogurt drink improved glycemic control in patients with type 2 diabetes: a randomized clinical trial. *Am J Clin Nutr.* 2011 Apr;93(4):764–71.

190. Ou HY, et al. Interaction of BMI with vitamin D and insulin sensitivity. *Eur J Clin Invest.* 2011 Nov;41(11):1195–1201.

191. Woods MN, et al. Effect of a dietary intervention and n-3 fatty acid supplementation on measures of serum lipid and insulin sensitivity in persons with HIV. *Am J Clin Nutr.* 2009 Dec;90(6): 1566–78.

192. Okuda Y, et al. Long-term effects of eicosapentaenoic acid on diabetic peripheral neuropathy and serum lipids in patients with type II diabetes mellitus. *J Diabetes Complications.* 1996 Sep-Oct; 10(5):280–87.

193. Singh U, Jialal I. Alpha- lipoic acid supplementation and diabetes. *Nutr Rev.* 2008 Nov;66(11): 646–57.

194. Davì G, Santilli F, Patrono C. Nutraceuticals in diabetes and metabolic syndrome. *Cardiovasc Ther.* 2010 Aug;28(4):216–26.

195. Larrieta E, et al. Pharmacological concentrations of biotin reduce serum triglycerides and the expression of lipogenic genes. *Eur J Pharmacol.* 2010 Oct 10;644(1–3): 263–68.

196. Kirkham S, et al. The potential of cinnamon to reduce blood glucose levels in patients with type 2 diabetes and insulin resistance. *Diabetes Obes Metab.* 2009 Dec; 11(12):1100–13.

197. Fenercioglu AK, et al. The effects of polyphenol containing antioxidants on oxidative stress and lipid peroxidation in type 2 diabetes mellitus without complications. *J Endocrinol Invest.* 2010 Feb;33(2):118–24.

198. Vuksan V, et al. Beneficial effects of viscous dietary fiber from Konjacmannan in subjects with the insulin resistance syndrome: results of a controlled metabolic trial. *Diabetes Care.* 2000 Jan; 23(1):9–14.

199. Sood N, Baker WL, Coleman CI. Effect of glucomannan on plasma lipid and glucose concentrations, body weight, and blood pressure: systematic review and meta-analysis. *Am J Clin Nutr.* 2008 Oct;88(4):1167–75.

200. Minich DM, Bland JS. Dietary management of the metabolic syndrome beyond macronutrients. *Nutr Rev.* 2008 Aug;66(8):429–44.

201. Pipe EA, et al. Soy protein reduces serum LDL cholesterol and the LDL cholesterol HDL cholesterol and apolipoprotein B: apolipoprotein A–I ratios in adults with type 2 diabetes. *J Nutr.* 2009 Sep;139(9):1700–6.

202. Yajima H, et al. Bitter acids derived from hops, activate both peroxisome proliferator-Activated receptor alpha and gamma and reduce insulin resistance. *J Biol Chem.* 2004 Aug 6;279(32):33456–62.

203. Krawinkel MB, Keding GB. Bitter gourd (Momordica Charantia): a dietary approach to hyperglycemia. *Nutr Rev.* 2006 Jul;64(7 Pt 1):331–37.

204. Kanetkar P, Singhal R, Kamat M. Gymnema sylvestre: a Memoir. *J Clin Biochem Nutr.* 2007 Sep; 41(2):77–81.

205. Hasani- Ranjbar S, et al. The efficacy and safety of herbal medicines used in the treatment of hyperlipidemia; a systematic review. *Curr Pharm Des.* 2010; 16(26):2935–47.

206. Katan MB, et al. Efficacy and safety of plant stanols and sterols in the management of blood cholesterol levels. *Mayo Clin Proc.* 2003 Aug;78(8):965–78.

207. Houston MC. Nutrition and nutraceutical supplements in the treatment of hypertension. *Expert Rev Cardiovasc Ther.* 2010 Jun; 8(6):821–33.

208. Walker AF, et al. Hypotensive effects of hawthorn for patients with diabetes taking prescription drugs: a randomised controlled trial. *Br J Gen Pract.* 2006 Jun; 56(527):437–43.

209. Tai MW, Sweet BV. Nattokinase for prevention of thrombosis. *Am J Health Syst Pharm.* 2006 Jun 15;63(12):1121–23.

210. Kasim M, et al. Improved myocardial perfusion instable angina pectoris by oral lumbrokinase: a pilot study. *J Altern Complement Med.* 2009 May;15(5):539–44.

211. Diabetes Prevention Program Research Group, et al. 10-year follow-up of diabetes incidence and weight loss in the Diabetes Prevention Outcomes Study. *Lancet.* 2009 Nov 14;374(9702): 1677–86.

212. Hyman MA. The failure of risk factor treatment for primary prevention of chronic disease. *Altern Ther Health Med.* 2010 May–Jun; 16(3):60–63.

213. Taylor AJ, et al. Extended- release niacin or ezetimibe and carotid intima-media thickness. *N Engl J Med.* 2009 Nov 26;361(22):2113–22.

214. Preiss D, et al. Risk of incident diabetes with intensive- dose compared with moderate-Dose statin therapy: a meta- analysis. *JAMA.* 2011 Jun 22;305(24):2556–64.

215. Grossniklaus DA, et al. Biobehavioral and psychological differences between overweight adults with and without waist circumference risk. *Res Nurs Health.* 2010 Dec; 33(6):539–51.

216. Galvin JA, et al. The relaxation response: reducing stress and improving cognition in healthy aging adults. *Complement Ther Clin Pract.* 2006 Aug;12(3):186–91.

217. Jorge ML, et al. The effects of aerobic, resistance, and combined exercise on metabolic control, inflammatory markers, adipocytokines, and muscle insulin signaling in patients with type 2 diabetes mellitus. *Metabolism.* 2011 Sep;60(9):1244–52.

218. Goodpaster BH, et al. Effects of diet and physical activity interventions on weight loss and cardiometabolic risk factors in severely obese adults: a randomized trial. *JAMA.* 2010 Oct 27;304(16): 1795–802.

219. Rosen RC, et al. Erectile dysfunction in type 2 diabetic men: relationship to exercise fitness and cardiovascular risk factors in the Look AHEAD trial. *J Sex Med.* 2009 May;6(5):1414–22.

220. Church TS, et al. Effects of aerobic and resistance training on hemoglobin A1c levels in patients with type 2 diabetes: a randomized controlled trial. *JAMA*. 2010 Nov 24;304(20):2253–62. Erratum in: *JAMA*. 2011 Mar 2;305(9):892.

221. Galletti PM, Joyet G. Effect of fluorine on thyroidal iodine metabolism in hyperthyroidism. *J Clin Endocrinol Metab.* 1958 Oct; 18(10):1102–10.

222. Xanthis A, et al. Advanced glycosylation end products and nutrition — a possible relation with diabetic atherosclerosis and how to prevent it. *J Food Sci.* 2007 Oct;72(8):R125-29.

223. Dolan M, Rowley J. The precautionary principle in the context of mobile phone and base station radiofrequency exposures. *Environ Health Perspect.* 2009 Sep; 117(9):1329-32.

224. Volkow ND, et al. Effects of cell phone radiofrequency signal exposure on brain glucose metabolism. *JAMA.* 2011 Feb 23; 305(8):808–13.

225. Genuis SJ. Fielding a current idea: exploring the public health impact of electromagnetic radiation. *Public Health.* 2008 Feb; 122(2):113–24.

226. Persky VW, et al. Effect of soy protein on endogenous hormones in postmenopausal women. *Am J Clin Nutr.* 2002 Jan;75(1):145–53. Erratum in: *Am J Clin Nutr.* 2002 Sep;76(3):695.

227. Galletti PM, Joyet G. Effect of fluorine on thyroidal iodine metabolism in hyperthyroidism. *J Clin Endocrinol Metab.* 1958 Oct;18(10):1102–10.

228. Schellenberg R. Treatment for the premenstrual syndrome with agnus castus fruit extract: prospective, randomised, placebo controlled study. *BMJ.* 2001 Jan 20;322(7279):134–37.

229. Estruch R. Anti- inflammatory effects of the Mediterranean diet: the experience of the PREDIMED study. *Proc Nutr Soc.* 2010 Aug;69(3):333–40.

230. Church TS, Earnest CP, Wood KA, Kampert JB. Reduction of C-reactive protein levels through use of a multivitamin. *Am J Med.* 2003 Dec 15;115(9):702–7.

231. Cani PD, Delzenne NM. The role of the gut microbiota in energy metabolism and metabolic disease. *Curr Pharm Des.* 2009; 15(13):1546–58.

232. Cecchini M, LoPresti V. Drug residues stored in the body following cessation of use: impacts on neuroendocrine balance and behavior — use of the Hubbard sauna regimen to remove toxins and restore health. *Med Hypotheses.* 2007;68(4):868–79.

233. Beever R. The effects of repeated thermal therapy on quality of life in patients with type II diabetes mellitus. *J Altern Complement Med.* 2010 Jun;16(6):677–81.

234. Kamenova P. Improvement of insulin sensitivity in patients with type 2 diabetes mellitus after oral administration of alpha-lipoic acid. *Hormones*. 2006 Oct–Dec; 5(4):251–58.

235. Wu G, et al. Arginine metabolism and nutrition in growth, health and disease. *Amino Acids.* 2009 May;37(1):153–68.

236. El-Ghoroury EA, et al. Malondialdehyde and coenzyme Q10 in platelets and serum in type 2 diabetes mellitus: correlation with glycemic control. *Blood Coagul Fibrinolysis*. 2009 Jun;20(4):248–51.

237. Sadruddin S, Arora R. Resveratrol: biologic and therapeutic implications. *J Cardiometab Syndr*. 2009 Spring;4(2):102–6.

238. Jiang WJ. Sirtuins: novel targets for metabolic disease in drug development. *Biochem Biophys Res Commun*. 2008 Aug 29; 373(3):341–44. Epub 2008 Jun 23.

239. Solerte SB, et al. Nutritional supplements with oral amino acid mixtures increases wholebody lean mass and insulin sensitivity in elderly subjects with sarcopenia. *Am J Cardiol.* 2008 Jun 2; 101(11A):69E–77E.

240. Yin J, Zhang H, Ye J. Traditional Chinese medicine in treatment of metabolic syndrome. *Endocr Metab Immune Disord Drug Targets.* 2008 Jun;8(2):99–111.

241. Xie JT, Mchendale S, Yuan CS. Ginseng and diabetes. Am J Chin Med. 2005;33(3):397–404.

242. http://www.yaleruddcenter.org.

243. http://online.wsj.com/article/SB124476804026308603.html

244. http://bostonreview.net/BR35.3/angell.php.

245. Adams KM, Kohlmeier M, Zeisel SH. Nutrition education in U.S. medical schools: latest update of a national survey. *Acad Med.* 2010 Sep;85(9):1537–42.

246. http://www.acpm.org/LifestyleMedicine.htm.

247. Tirosh A, Shai I, Tekes-Manova D, Israeli E, Pereg D, Shochat T, Kochba I, Rudich A. Israeli Diabetes Research Group. Normal fasting plasma glucose levels and type 2 diabetes in young men. *N Engl J Med.* 2005 Oct 6;353(14):1454-62. Erratum in: *N Engl J Med.* 2006 Jun 1;354(22):2401.

248. Gaziano JM, Hennekens CH, O'Donnell CJ, Breslow JL, Buring JE. Fasting triglycerides, highdensity lipoprotein, and risk of myocardial infarction. *Circulation*. 1997 Oct 21;96(8):2520-5.

249. Jessani S, Gangopadhyay K, Patel JV, Lip GY, Millane T. Should oral glucose tolerance testing be mandatory following acute myocardial infarction? *Int J Clin Pract.* 2007 Apr;61(4):680-3.

250. Gaby AR. Sub-laboratory hypothyroidism and the empirical use of Armour thyroid. *Altern Med Rev.* 2004 Jun;9(2):157-79.

251. Goglia F. Biological effects of 3,5-diiodothyronine (T(2)). *Biochemistry (Mosc).* 2005 Feb;70(2):164-72.

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