

BLOOD SUGAR PROBLEMS, INSULIN RESISTANCE, AND DIABETES

What's the Problem, and How Do You Diagnose It?

The process of digestion results in the release of glucose (a simple sugar) into the bloodstream. Normally, the pancreas then produces sufficient amounts of the hormone insulin to transport the glucose into the body's cells, thus maintaining a healthy blood sugar level. However, in some people the cells develop a decreased sensitivity to insulin, usually referred to as insulin resistance. This results in what is called glucose intolerance (a decreased ability to remove sugar from the blood). The body attempts to compensate by producing higher and higher amounts of insulin (shown in blood tests by high insulin levels, or hyperinsulinemia), but with serious insulin resistance, this may be inadequate to maintain a normal blood sugar. When the blood sugar remains too high (called hyperglycemia), the person will be diagnosed with diabetes. It is important to watch for the classic warning signs of diabetes: excessive thirst (especially thirst that doesn't seem to resolve when you drink water), abnormal hunger, and increased urination.

If blood sugar problems are not resolved, over time high blood sugar can cause damage to the blood vessels, and a long list of possible diabetic complications, including kidney failure, blindness, and problems resulting from cardiovascular disease (including strokes, amputations, and heart attacks). So far, the rate of development of diabetes in HIV+ people is relatively low, but researchers fear it may increase over time.

In some people, there may be times when the pancreas overproduces insulin, resulting in blood sugar that is too low (hypoglycemia). Low blood sugar can cause feelings of irritability, anxiety, nervousness, and intense hunger, as well as sweating. Waiting too long between meals can increase the possibility that blood sugar may drop too low at certain points, especially in those who have tendencies toward chronic hypoglycemia. With more and more HIV+ people developing blood sugar problems and, in some cases, diabetes, hypoglycemia may become more common. We tend to talk much more about high blood sugar, but too low blood sugar is also a serious problem, and always zaps energy. Initially, when the blood sugar drops too low, the brain is not getting the energy it needs, and the result is a feeling of serious fatigue, along with irritability and emotional swings due to the release of adrenal hormones. Many people suffering from hypoglycemia experience a roller coaster effect as their blood sugar bounces from low to high to low again, with multiple episodes throughout the day. This can contribute significantly to feelings of overall fatigue. Each time the blood sugar drops too low, there can be a serious loss of energy. Then, because the low blood sugar causes a craving for food, many people resort to quick-fix snacks that contain substantial sugar. This rush of glucose will temporarily raise the blood sugar but in many cases, the level goes too high and the pancreas may respond to the sudden increase by over-producing insulin. This, in turn, lowers the blood sugar too much and results in another bout of hypoglycemia symptoms. During each of these episodes, insulin escorts tryptophan into the brain which then stimulates the creation of serotonin, the sleep chemical. This inevitably results in additional feelings of fatigue.

The diagnosis of blood sugar problems is made by doing a fasting glucose (measuring blood sugar after an overnight fast) and a hemoglobin A1C (which is a blood test used to estimate the average glucose level over the last 3 months or so). An oral glucose tolerance test may also be done in order to assess your body's response to glucose. Blood levels of insulin can also be measured to check for hyperinsulinemia.

If your physician wants to see the pattern of your blood sugars over time, s/he may recommend that you use a blood sugar meter to test your own blood sugar several times daily. This requires using an instrument that looks something like a pen in order to jab yourself to draw blood (not as painful as it sounds) and then allowing the meter to read the blood to establish your blood glucose level. Your physician will probably ask you to keep a record of the results over time; some meters have the capacity to keep such records.

What are the Causes?

Protease inhibitors have been tied to an increased incidence of glucose intolerance and decreased sensitivity to insulin. Research has shown that indinavir (Crixivan®), amprenavir (Agenerase®) and ritonavir (Norvir®) (and possibly other protease inhibitors) suppress insulin-stimulated glucose uptake by inhibiting the transport activity of the proteins that normally move glucose from the cell surface into the fat and muscle cells. The researchers, noting that other studies have shown that insulin resistance appears prior to the appearance of lipodystrophy symptoms, theorize that insulin resistance may occur much earlier than has been so far reported, may be far more widespread, and may be at least one of the causes of lipodystrophy. Both this and the other theories so far proposed to explain the tie between PIs and insulin problems are complex, and additional research will be required to fine tune our understanding of this.

In general, the risk for diabetes is higher in those with a family history of diabetes, those who are overweight, and those who don't exercise regularly. Anyone currently taking a protease inhibitor who also has one or more of these risk

factors should be particularly scrupulous about monitoring blood glucose and watching for warning signs of blood sugar problems.

What are the Treatments?

For anyone with beginning evidence of blood sugar problems, it will be important to discuss with your physician the possibility of switching from a protease inhibitor-containing HAART combo to a non-PI regimen. It will also be important to immediately begin the non-drug therapies (dietary changes, exercise, nutrient supplementation, weight loss, if needed, and hormone replacement, if needed) that can help improve insulin sensitivity. Blood glucose should be regularly monitored to see if such approaches are sufficient to normalize blood sugar. When they are not, drug therapies to normalize glucose should be discussed with your physician.

There has been almost no research to date looking at ways to improve insulin sensitivity in HIV+ people other than through switching antiretrovirals, or using anti-diabetic drugs. However, in non-HIV+ people, years of research and many very large studies have shown the value of dietary changes, exercise, and weight loss for improving blood sugar control. Smaller studies have also shown the value of various nutrients for improving insulin sensitivity and normalizing blood sugar. Thus, it would seem very appropriate to incorporate these non-drug approaches into any program aimed at improving blood sugar. With an aggressive combination of dietary changes, exercise, weight loss, if necessary, and appropriate nutrient supplementation and hormone replacement, it may be possible for many people to avoid the use of the anti-diabetic drug therapies (each of which comes with its own set of side effects).

Key Treatments

Switching drugs. Substituting an NNRTI (non-nucleoside analogue reverse transcriptase inhibitor) or an NRTI (nucleoside analogue reverse transcriptase inhibitor) for a protease inhibitor has been suggested as a possible way to improve insulin sensitivity. The switch studies done to date have been somewhat conflicting but there is some evidence that switching from a protease inhibitor to either nevirapine (an NNRTI) or abacavir (an NRTI) may improve insulin sensitivity and lower glucose levels. Results with a switch to efavirenz have been less clear, with one study showing improvement and another not. Much more research will be required to determine what really may be best in this regard. It will be very important to consider the treatment history for anyone considering switching drugs, since some people may really need the protease inhibitor(s) to maintain viral control.

Exercise. It can't be said strongly enough: exercise is HUGELY important for increasing insulin sensitivity and reducing blood sugar. Countless studies in non-HIV+ people have shown that insulin sensitivity is greatly increased with regular exercise. Both weight training (such as lifting weights) and aerobic exercise will help. For the best results, combining every other day weight training with daily aerobic exercise (brisk walking, swimming, stair-stepping, jogging, using a treadmill or rowing machine or other aerobic device, or anything else that gets your heart pumping and muscles moving) may be ideal. [For much additional information on exercise for HIV+ people, see *NYBC's Self-Care Guide*.]

Weight loss. For those who are overweight, losing weight can be very helpful in improving insulin sensitivity and decreasing the risk of developing diabetes. Discuss this with your physician and get the help you need to achieve needed weight loss.

Dietary improvements. Increasing the intake of fiber by eating more whole-grain foods (like brown rice instead of white, whole-grain breads and crackers and pastas instead of white, and so on), beans, and fruits and vegetables is important, as is using healthful fats (mostly monounsaturated fats like olive oil or walnut oil or almond oil, as well as walnuts, almonds, flaxseed, pumpkin seeds, and pecans). Increasing your fiber intake by consuming more dark green vegetables (spinach, Swiss chard, broccoli, mustard greens, kale, and so on) rather than focusing on an increase in starchy grain foods will have a more positive influence on regulating blood sugars. One multi-center study (*Clin Infect Dis* 2001;33:710-717) found that both a higher intake of polyunsaturated fats (like corn oil and safflower oil and all the foods made with such polyunsaturated fats) and a lower intake of dietary fiber were strongly associated with insulin resistance.

Decreasing the intake of sugar and all the countless snack and dessert foods made with it, and the intake of white foods (white rice, white flour and all the breads, crackers, cookies, and snack foods made with it) is also important since these low-fiber foods tend to increase the blood sugar much more than high-fiber foods. Accompanying the intake of carbohydrate foods with some protein and fat will also help since the latter will slow the digestion of the carbohydrates, and thus slow the release of glucose into the bloodstream. It may also help to eat four to six small meals daily, rather than two or three big ones. Research in non-HIV+ people has shown that spreading food intake across the day this way helps to improve glucose tolerance and stabilize blood sugar.

Stevia, an alternative herbal sweetener available at most whole foods supermarkets or health food stores, can be an effective substitute for sugar. It's a white powder which tastes sweet but is plant-derived (no nasty chemicals), does *not* contain glucose, and will not raise blood sugar. It can be used any place that sugar would be used, but in lower amounts since it actually tastes sweeter than sugar. Just be careful of which product you choose. Some manufacturers add saccharine or other artificial sweeteners to stevia so read labels carefully and make sure you choose a product that contains nothing but stevia itself.

Strict avoidance of partially hydrogenated fats (often called "trans" fats) is crucial. These are chemically modified fats that are found in most margarines, vegetable shortening, and a large percentage of commercial baked goods (including most breads, crackers, cookies, pastries, etc.) and snack foods. Everyone who cares about insulin resistance and protecting their cardiovascular system needs to read labels (look for the words "partially hydrogenated" followed by any oil) and try to avoid these artery-damaging and cell-stiffening fats to the greatest extent possible. These partially hydrogenated fats have a rigid structure. If you consume them, they will be incorporated into cell membranes (the outer layer of cells) and cause a stiffening and dysfunction of both the membrane and the receptors within the cell membrane, including insulin receptors. The result can be increased insulin resistance. Another variety of bad fats are oxidized fats (any oil that has been heated to very high temperatures, particularly when it is re-used over and over, and, thus, all the fried foods made with such oils). These oxidized fats cause cell membrane damage in a different way, and can also harm cellular and receptor function.

Instead of these damaging fats, stick with the fats Mother Nature made, especially the monounsaturated fats like olive oil. If flavor is an issue to you in terms of oil choices, note that olive oil is available in the more full-flavored green varieties, as well as in lighter versions that have little or none of the usual olive taste. For baking or other cooking where you don't want the traditional olive oil flavor, the latter would be a good choice. There are other monounsaturated oils that would be good choices, including walnut oil and almond oil. However, some of the other monounsaturated oils are less desirable. For example, canola oil is heavily processed (using heat and chemicals) in ways that make it less appealing for those seeking the best oil for cardiovascular health.

To find baked goods and snack foods that don't contain the bad fats, you may need to seek out a whole foods supermarket or one of the large supermarket chains (Safeway and King Sooper's and other national chains) that now carry a substantial amount of "health foods" or "natural foods." Luckily, some of these stores now have entire aisles of healthy foods, and their bread sections include some of the organic whole-grain breads that generally don't have any of the partially hydrogenated fats on their lists of ingredients.

One dietary change that may be particularly important is to aim for foods lower on the "glycemic index" scale. The glycemic index ranks foods based on how they affect blood sugar levels by measuring how much blood sugar increases in the two or three hours after eating them. Since foods that are high in fat or protein have much less effect on blood sugar, the glycemic index concept is generally only used for foods high in carbohydrates.

Using the glycemic index list of foods is useful because not all carbohydrates act the same. Foods that have a high glycemic index are quickly broken down in the intestine, causing the blood sugar level to rise rapidly. Foods that have a low glycemic index are broken down more slowly, giving the body a better chance to maintain normal blood sugar. Contrary to what scientists had once believed, research done to test the glycemic index of foods has shown that some complex carbohydrates may actually cause the blood sugar to rise more rapidly than simple sugars. For example, baked potatoes have a glycemic index considerably higher than that of table sugar. For someone with blood sugar problems, sitting down to a plain baked potato may be worse than eating a chocolate bar. There are many other surprises on the list, and the bottom line is that you will need to use researchers' findings rather than your best guess to determine which foods may have the greatest effect on your blood sugar. Not all foods have been tested, but a current list of the glycemic index of many foods is available at www.mendosa.com/gilists.htm (For more on specific diet suggestions, see NYBC's Self-Care Guide.)

Nutrient supplementation. Supplementation with the nutrients that help maintain normal cellular insulin sensitivity and improve glucose tolerance may help. Included are alpha-lipoic acid, the B vitamins, especially B-6, and the minerals chromium and zinc. Supplementation with antioxidants may also be useful.

Alpha-lipoic acid is an antioxidant that has been shown to increase insulin sensitivity and help reduce blood sugar in non-HIV+ people with Type 2 diabetes. Doses of 200-400 mg, three times daily, preferably taken on an empty stomach, may be useful. Use of a time-released formula is advisable because this nutrient has a very short half-life (meaning that it disappears from the bloodstream quite rapidly).

Chromium is a mineral that has been shown to improve glucose tolerance in non-HIV+ people. There are formulas available that contain what is called the glucose tolerance factor (GTF), a chromium-containing molecule which

is very important in the regulation of carbohydrate metabolism. Supplementation with GTF has been shown to improve glucose tolerance in non-HIV+ people. Taking one GTF formula capsule, containing 200 mcg of chromium, with each meal may be useful.

Vitamin B-6 is used in the body's regulation of the breakdown of glycogen into glucose, an important factor in the body's ability to maintain normal blood sugars. Deficiencies of B-6, known to be common in HIV+ people, can lead to impaired glucose tolerance. Thus, supplementation with B-6 (50 mg, three times daily with meals) may help improve glucose tolerance. As with all other individual B vitamins, it should always be used in conjunction with a B complex formula.

Zinc deficiency is known to cause impaired glucose tolerance. Because researchers have shown that this mineral is frequently deficient in HIV+ people, supplementation with doses of 25 to 50 mg daily may help. Zinc supplementation should always be balanced with intake of copper (3 to 5 mg daily, taken at a meal other than the meal with which zinc is taken).

Antioxidants (especially vitamins C and E, alpha-lipoic acid, N-acetyl-cysteine, selenium, carotenoids, bioflavonoids, and coenzyme Q-10) may be important for anyone with elevated blood sugar. Researchers have reported that the underlying mechanism by which high blood sugar may cause arterial problems (and, thus, all the complications that result from that) is oxidative stress, the condition that antioxidants counter. Thus, regular intake of all the important antioxidants may help prevent such long-term complications, even in those in whom blood sugar problems cannot be fully corrected. Appropriate oxidative stress-counteracting doses might be vitamin E (800 to 2,000 IU daily), vitamin C (2,000 to 6,000 mg daily, spread across three meals), bioflavonoid complex (1 capsule with each meal), carotenoid complex (1 capsule with each meal), selenium (400 to 600 mcg daily, total from all sources, including your multiple), coenzyme Q-10 (100 to 500 mg daily), N-acetyl-cysteine 500mg (1500 to 3000mg daily), and alpha-lipoic acid (200 to 400 mg, three times daily). For more detail on these nutrients, see *NYBC's Core Nutrient Protocols* in this Guide's *Introduction*.

B-6 Pyridoxyl-5-Phosphate 50mg x 100	3/d (1B, 1L, 1D)
Chromium GTF 200mcg x 100	3/d (1B, 1L, 1D)
OptiZinc 30mg x 100	1/d (plus multivitamin, mineral ascorbates C)
Antioxidants	see NYBC Core Protocols in Introduction

Botanicals.

Bitter Melon (*Momordica charantia*). The fruit and leaves of this plant are most often used. Regulates blood sugar levels. Antiviral effects from fruits, seeds, leaves and vines. Hot water and alcohol extracted. Each gram is equal to 25 grams of whole plant. Not standardized to any particular protein (e.g., MAP-30). Do not use during pregnancy.

Clinical Nutrients for Diabetics (Phytopharmica) is specially formulated for individuals with elevated blood sugars. Ingredients include vitamins C (as ascorbic acid), E, B6, B12, folic acid, biotin, magnesium, zinc, selenium (aspartate), copper (picolinate), manganese, chromium (picolinate), sodium, vanadyl sulfate as well as a mix of herbs including *Gymnema sylvestre* leaf extract (standardized to contain 24% gymnemic acid), a whole fruit extract of bitter melon (*Mormordica charantia*), fenugreek (*Trigonella foenum-graecum*), bilberry (*Vaccinium myrtillus fructus*, standardized to 25% anthocyanosides, calculated as anthocyanidins), and some mixed bioflavonoids (citrus). See the information in the separate entries for *Gymnema sylvestre*, bitter melon and fenugreek. Some suggest that vanadyl sulfate is not a very good idea for people with HIV. Be sure to double check multivitamins and other blends you may be taking to make sure this doesn't increase your daily intake of vanadium, selenium or zinc. For example, at the suggested dose, that's 100 mcg of selenium in addition to whatever other sources you may be taking. *Note: NYBC is not yet carrying this item.*

Gymnema Silvestre. A climbing plant found in central and southern India and used in Ayurvedic practice to normalize excessive blood sugar levels. (It has no effect on normal levels.) It apparently helps the pancreas to produce insulin. May also act as a diuretic. **Do not take with other glucose-moderating drugs or insulin.**

Vanadyl Sulfate. This may have liver toxicities and should be avoided by those on either liver toxic drug regimens or who have other underlying liver disease. The mineral vanadium is used in the body to regulate the cell's sensitivity to insulin. Many multivitamins already contain a certain amount of vanadium, usually in this form. It also plays an important role in fat and bone metabolism.

NYBC and Other Nutraceuticals for Blood Sugar Support:

Bitter Melon 500mg x 100	6/d (2B, 2L, 2D)
Clinical Nutrients for Diabetics x 90	3/d (1B, 1L, 1D)
Gymnema Silvestre 500mg x 90	3/d (1B, 1L, 1D)
Vanadyl Sulfate 7.5mg x 90	3/d (1B, 1L, 1D)

Hormone replacement. In men whose blood tests show testosterone deficiency, replacement therapy with testosterone, delivered through the skin via gels or patches, may help increase insulin sensitivity. Ask your physician to test your testosterone levels. Note that although testosterone replacement may be needed by women for other reasons, it will not increase insulin sensitivity in women. (For additional information on hormone replacement therapy in HIV+ people, see NYBC's *Self Care Guide*.)

Drug Therapies. If blood sugar monitoring shows that your blood sugars are rising unacceptably, and lifestyle modifications or drug switches are not enough to get blood sugar under control, anti-diabetic medications may be needed. Two common drugs are rosiglitazone (Avandia) and metformin (Glucophage). Studies on the use of such drugs with PI-caused insulin resistance are limited but have shown improvements. In one trial, people given 850 mg of metformin, three times daily, achieved significant drops in fasting glucose, insulin, and triglycerides, along with small but significant (compared to placebo) drops in visceral fat, but the high dose caused severe diarrhea and abdominal cramps in some. And it's important to note that this dose of metformin also resulted in loss of subcutaneous fat in these people, making it inadvisable for those with lipoatrophy (fat loss in the face, arms, legs, or buttocks).

In another study, a lower dose of 500 mg of metformin, twice daily, resulted in significant drops in insulin levels, as well as decreases in overall weight and diastolic blood pressure, and small (but not significant compared to placebo) drops in visceral fat. Anyone considering metformin should be aware that it can cause lactic acidosis, a rare but potentially lethal side effect of nucleoside analogue drugs. Whether combining multiple agents (metformin and nukes) that have the potential to cause this problem would increase the overall risk of developing lactic acidosis is not clear, but be forewarned of the possibility.

As opposed to metformin's tendency to cause fat loss, the glitazone drugs (rosiglitazone and pioglitazone) are known to actually cause fat cells to be added, at least in the HIV-negative, making them possibly a better choice for those who have both insulin resistance and fat loss problems. One small pilot study of troglitazone (Rezulin) showed improved insulin sensitivity, increased lean body mass, decreased visceral fat, and increased subcutaneous fat (just what somebody with combined fat accumulation and fat wasting problems would want) in those taking the drug. However, troglitazone has been taken off the market due to liver toxicity, and later studies done with rosiglitazone so far have not shown improvements in either reducing visceral fat accumulation or restoring subcutaneous fat loss, although insulin levels have decreased, an indicator that insulin is being better used. Additional studies are ongoing, including one that is combining metformin with rosiglitazone to see if the glitazone effects will counter the tendency of metformin to reduce subcutaneous fat.

Most expert groups are waiting for additional research before making official recommendations on approaches to handling insulin resistance and blood sugar problems in HIV+ people, but the **British HIV Association now recommends the following:**

For anyone with symptoms of glucose intolerance:

- dietary advice and exercise
- switch PI to PI-sparing regimen (in people taking their first regimen)

For measurable glucose intolerance (fasting glucose 101 to 115 mg/dL or two-hour glucose tolerance test 117 to 185 mg/dL) with body mass index above 25 mg/kg², insulin above 17 mU/L, and hemoglobin A^{1C} above 6.5 mU/L):

- consider metformin (500 mg twice daily)
- switch off PI

For anyone with diabetes (fasting glucose above 117 mg/dL random value or two-hour glucose tolerance test above 185 mg/dL with the same additional parameters that are listed above)

- metformin (500 mg twice daily)
- review after three months

For anyone with body mass index 18 to 25 mg/kg² with insulin above 17 mU/L and hemoglobin A^{1C} above 6.5 mU/L

- sulphonylurea therapy
- consider metformin (500 mg twice daily)

For anyone with body mass index below 18 mg/kg² with lipoatrophy, insulin above 17 mU/L, and hemoglobin A^{1C} above 6.5 mU/L

- consider rosiglitazone (2 to 5 mg daily) or pioglitazone
- seek clinical opinion

To obtain the Brits' most up-to-date recommendations on how to handle glucose intolerance, go to the British HIV Association website at www.bhiva.org.