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Herbs and insulin resistance

by Paul Bergner

Abstract: The increasing recognition of the pathological effects of hyperinsulinemia with and without loss of glycemic control has led to the search for agents that increase insulin sensitivity in preference to those that stimulate insulin secretion or inhibit liver production or release of glucose in order to lower blood glucose in Type II diabetes (NIDDM) or to improve the profile of hyperinsulinemia and dyslipidemia in insulin resistance syndrome without diabetes. The mechanisms of action of pharmaceutical drugs and twelve herbal medicines that lower blood glucose are reviewed. *Panax ginseng*, *Gymnema sylvestre*, *Brickellia* spp *Vaccinium* spp and *Syzygium jambolana* appear to lower blood glucose through undesirable mechanisms. *Panax quinquefolius*, *Foeniculum vulgare*, *Grifola* spp *Momordica charantia*, *Ocimum* spp and *Cinnamomum cassia* may act at least in part by increasing insulin sensitivity in the tissues.

Introduction

Insulin resistance has been recognized as the root pathology underlying Type II diabetes (Non Insulin Dependent Diabetes Mellitus, or NIDDM) for decades, but only in recent years has insulin resistance syndrome (IRS) without loss of control of blood glucose been recognized as a major disease pathology in its own right. When the cells become resistant to the effects of insulin, the pancreas secretes larger amounts, and for a longer period of time. Figure 1 (page three) shows typical insulin curves after a glucose challenge in a variety of patients. The top curve is for an individual who may have perfectly normal fasting and post-meal blood glucose levels. The second curve shows a similar individual whose IRS has progressed to loss of glycemic control. This patient still has hyperinsulinemia, with the added pathological burden of elevated blood glucose. Both patients have elevated and prolonged insulin curves compared to the third curve, for an individual with both normal insulin and blood glucose levels. Research from the last decade

Asthma case study

Chanchal Cabrera, M.N.I.M.H., M.Sc.

Abstract: A 36 year-old patient with asthma of 6 years duration was successfully weaned from prescriptions of Ventolin and Becloforte using a combination of herbal therapeutics and withdrawal of milk products from the diet. The patient was medication-free after several months and remained so for a year of follow-up.

Patient

Female. Aged 36. Presented with asthma which began 6 years ago during her 2nd pregnancy. She had a long history of repeated sinus infections and bronchitis and had received many antibiotics and steroids over the years. She was presently using Ventolin 5 - 10 puffs a day and Becloforte 2 puffs twice day. She felt a chest tightness all the time and all exertion was difficult. She had a lot of family stress and had a history of depression. There was a family history of eczema and allergies. On examination her chest expansion was greatly reduced and there was a slight expiratory wheeze. She had once been hospitalized for status asthmaticus and was afraid of this happening again.

Recommendations

She was advised to quit eating all dairy products and any foods with dairy in them and to avoid all sweetened and sugary foods and all processed or packaged foods. She was given information on avoiding dairy, reducing exposure to dust and airborne allergens, and on breathing exercises.

Supplements

Vitamin C to bowel tolerance

Evening Primrose oil 3 g./day

N-acetyl-cysteine 1500 mg./day

Quercetin 1 g./day

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Insulin resistance from page one

has demonstrated that such elevated insulin, with accompanying metabolic factors, is a root cause of many of the diseases of modern civilization even in the absence of overt diabetes.

Pathophysiology of hyperinsulinemia

In normal metabolism, as insulin rises after a meal, or in response to stress-related hyperglycemia during periods of stress, it triggers release of insulin-like growth factor (IGF-1) from the liver. This in turn suppresses growth hormone, and IGF-1 effects combine with those of insulin for a net anabolic effect on cells. The combination of elevated or prolonged insulin secretion in IRS, the accompanying excessive and prolonged secretion of IGF-1, with extended suppression of growth hormone can have powerful pathological effects on the tissues. Some chronic conditions related to insulin resistance and compensatory hyperinsulinemia, but with normal glycemic control, are listed below.

Obesity

Hypertension

Atherosclerosis

Elevated triglycerides with depressed HDL cholesterol

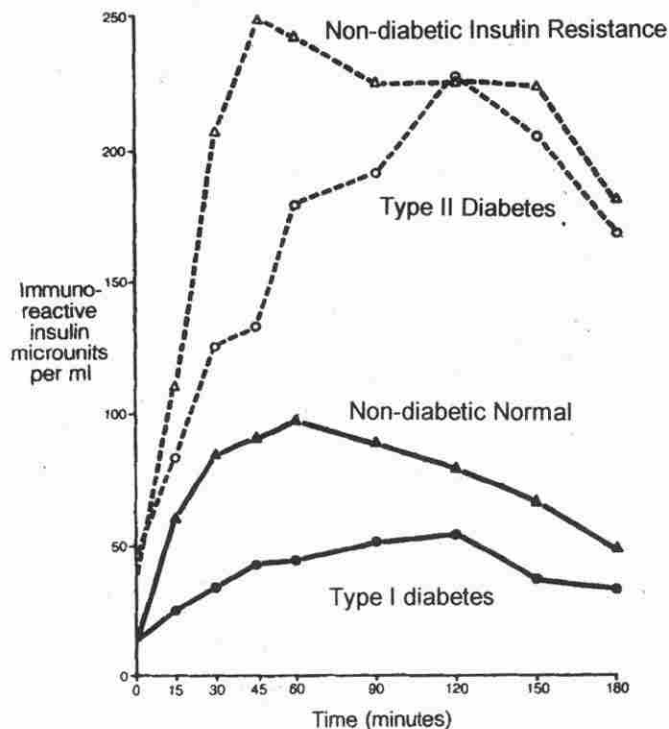
Increasing the tendency of the blood to clot

Heart attacks and strokes

Polycystic ovarian syndrome

Elevated IGF-1 accompanying insulin resistance may also be related to the pathology of cancers of the breast, prostate, and colon.

All the above may occur in an individual with normal control of blood sugar. In NIDDM, elevated blood glucose may add to the damage, but simple reduction of blood glucose will not remedy the problem. Both insulin and blood glucose must be lowered, preferably by correcting the original resistance of the cells to the effects of insulin. Glycemic control in diabetes attained through stimulation of insulin in a patient who is already hyperinsulinemic may worsen the prognosis of the disease or threaten serious hypoglycemic episodes. Agents that suppress liver production or release of glucose have historically led to liver disease in some patients, and at least three leading drugs in this category had to be pulled from the market due to hepatotoxicity.



The patient above with the highest insulin curve has normal blood glucose. In the patient with NIDDM, therapies that normalize blood glucose by elevating insulin worsen the underlying pathology of diabetes. (Bagdade et al.)

Natural methods to increase insulin sensitivity

Drug or herbal treatments to correct insulin resistance and hyperinsulinemia are irrational as permanent cures, because the syndrome is easily treated with lifestyle and dietary modification. A combination of reduction of carbohydrates in the diet, regular moderate activity including cross training to tone multiple muscle systems, and supplementation with nutritional factors known to increase insulin rapidly improve measures of insulin resistance, including glycemic control in NIDDM. Some nutritional factors that may increase insulin sensitivity are listed below.

Chromium picolinate 200-400 mcg twice a day

Cod Liver Oil for a dose of docosahexaenoic acid (DHA) equivalent to 2-4 grams/day

B-Complex, in the form of a multivitamin

Magnesium 600-1000 mg/day

Zinc 30-60 mg/day

Drug actions

Drugs that lower blood glucose may do so in the following ways:

Reduce glucose absorption from the intestine.

This must be viewed as a poor substitute for reducing carbohydrates in the diet.

Inhibit liver enzymes that release glucose from the liver. This may be either through suppression of the release of glucose from glycogen, or of manufacture of glucose through gluconeogenesis. Drugs of this class have potential liver toxicity as a side effect. This action does not address the underlying pathology of insulin resistance, but creates a disease condition in the liver to balance the disease condition in the cells.

Stimulate insulin production or release from the pancreas. This approach may lower blood glucose, but actually worsens the underlying pathology. The accompanying graph shows that insulin is already pathologically elevated in NIDDM. The hyperinsulinemia itself is pathogenic and produces many of the destructive symptoms of NIDDM. Stimulating it further may also hasten the ultimate exhaustion of the pancreas. Drugs which powerfully elevate insulin also increase the risk of fatal hypoglycemic events.

Increase insulin sensitivity. If a drug or herb is used for IRS or NIDDM, this should be the preferred effect. This should not, however, be expected to take the place of normal nutritional components or normal activity that decreases insulin resistance.

Pharmaceutical drugs

The quest for oral hypoglycemic agents was to prevent the inconvenience of insulin injections. For most of the later twentieth century the focus was on lowering blood glucose, without particular regard to the mechanism. With a growing understanding of insulin resistance as the underlying mechanism of a syndrome that is pathological in itself whether or not it includes loss of glycemic control, the focus in the recent decade has been to identify drugs that increase insulin sensitivity.

Guanidine derivatives

First oral hypoglycemic drugs were guanidine derivatives. These may have a combination effect of suppression of sugar production in the liver and increase in insulin sensitivity in the cells. The first drugs in the class, buformine and phenformine, were discontinued due to adverse effects on the liver. The current drug in this category is metformin (Glucophage).

Sulfonureas

The next generation of oral hypoglycemics are the sulfonureas. These increase pancreatic insulin, and symptomatically reduce blood sugar. These drugs can cause life-threatening hypoglycemia. They also elevate triglycerides, a normal consequence of hyperinsulinemia. They hasten the degeneration of the pancreatic insulin-producing cells in NIDDM. They are contraindicated in pre-diabetic insulin resistance due to the tendency to cause hypoglycemia.

Thiazolidinediones

Troglitazone (Rezulin) was widely heralded in the mid-nineties as an insulin-sensitizing agent, but eventually was withdrawn from the market after nearly 100 cases of acute Liver Failure developed in people taking it (Graham et al.).

Metformin

Metformin (Glucophage) is a guanidine derivative that inhibits liver production of glucose via gluconeogenesis, and also increases the insulin sensitivity of the peripheral tissues. It does not cause hyperinsulinemia or hypoglycemia and may be the most appropriate drug therapy where a drug is required to control blood glucose. It is widely promoted as an insulin sensitizer, but it also acts on the liver, has multiple side effects, and may cause death in individuals with impaired kidney function, a common condition in diabetes.

A study of representatives of the guanidine derivative and sulfonureas in 1971 found that although they improved control of blood glucose, they significantly increased deaths from cardiovascular causes relative to giving insulin alone (Cornfield; Schor; University Group Diabetes Program.).

Herbs

Many herbs have been used to treat diabetes or its symptoms in areas of the world and in eras when diabetes was present. Diabetes apparently first appeared in ancient Egypt, followed later in the grain farming valleys of India, China, and Mesopotamia. The first recorded case in European history appears to be in the 1600s in Holland. Some of these herbs reduce blood glucose, and others treat the symptoms of diabetes without lowering blood glucose. Considering current understanding of insulin resistance, the same discrimination should be used when selecting herbs that lower blood glucose as when selecting drugs. Herbs that

lower blood glucose by increasing insulin sensitivity may also be useful in IRS without diabetes. Many historical and currently popular herbs for lowering blood sugar do so through worsening the underlying state of hyperinsulinemia.

Panax

Various studies of both Asian and American ginseng have shown improvement in aspects of glycemic control in animals and humans. The mechanisms are not clear, but at least some constituents of *Panax ginseng* promote insulin production and release, and improvements in control of blood of glucose may be at the expense of stimulating hyperinsulinemia (Waki et al.; Kimura et al.).

A low dose of *P. ginseng* (100-200 mg) extract was given to 36 diabetic subjects for 8 weeks. The test groups showed improvements in fasting blood glucose and increases in daily activity and exercise. No mechanism was suggested for the activity, but there was no change in serum lipids in the ginseng group. If the action were through improving insulin sensitivity, a drop in serum triglycerides would be expected, so it appears that ginseng acts through methods other than the optimal increase of insulin sensitivity in the peripheral tissues (Sotaniemi et al.).

Oral administration of an oral preparation of unprocessed roots of *P. ginseng* in mice reduced blood glucose. The mechanisms suggested were through inhibition of intestinal glucose absorption, and suppressing liver production of glucose, the latter being an undesirable mechanism for long term use (Chung et al.).

A preparation of *P. ginseng* rootlets lowered blood glucose in animals, and the suggested mechanisms were inhibition of intestinal absorption of glucose, and an increase in insulin sensitivity. *P. ginseng* rootlets are considered a separate medicine from the root in Chinese herbalism, with rootlet actions resembling the yin tonic American ginseng (*Panax quinquefolius*) rather than the more stimulating chi and yang tonifying effects of *P. ginseng* (Chung et al.).

One gram doses of American ginseng reduced the area under the blood glucose curve in human volunteers without diabetes. The effect was statistically significant, but was slight, from 12-19% of the area under the curve. The ginseng had to be given at least 40 minutes before the glucose challenge to be effective, and a 3 gram dose provided no improved results over a 1 gram dose (Vuksan et al. 2001).

The same researchers found a clinically significant fall in the peak glucose level at the 2 hour point in patient with NIDDM, with administration of 3 gram of *P. quinquefolius* – blood glucose at the 2 hour point was 60% lower in the panax group than the placebo group (Vuksan et al. 2000b).

In an earlier trial, in both insulin-resistant diabetics and non-diabetic overweight individuals, the researchers found that a 3 gram dose given 40 minutes before a glucose challenge reduced the area under the post-meal glucose curve by just less than 20% (Vuksan et al. 2000a).

No mechanism has been suggested for the activity of American ginseng. The demonstrated insulin secretagogue effects constituents of *P. ginseng* roots suggest that it should be avoided in the treatment of insulin resistance. Insulin-sensitizing *P. ginseng* rootlets are generally not available in the U.S. herb market, but their traditional use as an analogue to *P. quinquefolius* at least suggests that *P. quinquefolius* should be used

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in preference to *P. ginseng* for insulin resistance syndromes.

Gymnema

Gymnema sylvestre is a traditional Ayurvedic and Arabic medicine used for diabetes since antiquity in India (Nadkarni) and Egypt (El Gammel). Clinical trials have shown that it can lower blood sugar in both Insulin Dependent Diabetes (IDDM) and NIDDM (Shanmugasundaram et al.; Baskaran et al.). Typical conventional dose: 10 to 15 ml per day of a 1:1 extract or Gymnema tablets 4000 mg 3 daily. Research into the mechanism of action in animals suggests that the plant delays the absorption of glucose from the intestine (Yoshikawa et al.; Shimizu et al.). Consistent results in petrie dish, animal and human trials demonstrate that it increases insulin secretion (Persaud et al.), raises serum insulin (Shanmugasundaram et al.; Baskaran et al.), and does not act through increasing insulin sensitivity in the tissues (Tominaga et al.). Older research show that the plant can induce hypoglycemia in normal animals (Nadkarni). Thus gymnema has qualities in common with the sulfonureas drugs. It lowers blood sugar by worsening the underlying disease process of hyperinsulinemia.

Vaccinium

The leaves of *Vaccinium myrtillus* and related species (blueberry, bilberry) have been used to treat diabetes and its complications since antiquity in Egypt (El Gammel). They are also used in Central European folk medicine (Weiss; Petlevski). The use for diabetes in the U.S. appears to have been first recorded in the 1930s, when researchers found it used Swiss-American folk medicine, and verified a blood sugar lowering effect; by the 1960s it had entered into common usage as a treatment for elevated blood sugar in the U.S. via the health foods industry (Crellin and Philpott). In both traditional and contemporary literature, distinction has to be made between use of the leaf and the berry. *Vaccinium* berry and its flavonoid extracts are used to treat the vascular damage of diabetes without altering insulinemic or glycemic status (Savickiene et al.).

No studies appear to describe a mechanism for its action, but Weiss reports research showing that long-term use can cause severe hydroquinone poisoning and states that it is not appropriate for regular use. Weiss does not state the form or dose that may cause poisoning. Appalachian herbalist Tommie Bass states that the dose he recommended was several hands full

of the leaf in a gallon of water to make tea and makes no observation of toxicity (Crellin and Philpott).

Oplopanax

Oplopanax horridum (devil's club) has a reputation among contemporary herbalists as a plant that can lower blood sugar in diabetes. The first report of this historically was based on an anecdote in British Columbia where a native coming to a hospital for surgery suddenly developed the symptoms of diabetes. The physician enquired and it seems that the man had been taking devil's club. The doctor postulated that the devils club was effectively treating the diabetes, and when the plant was withdrawn in the hospital, the full disease emerged. The case was written up and published in a Canadian medical journal. The problem with this particular anecdote is that borderline NIDDM often appears only under conditions of stress, and then disappears when the stress is removed. An aboriginal man admitted to a hospital for anesthesia and surgery could have been experiencing severe stress, and this could have caused the emergence of the symptoms of NIDDM rather than withdrawal of the oplopanax. Subsequent clinical trials have found no effect of oplopanax on either blood sugar or insulin (Justice; Thommassen et al.).

A review of the older ethnobotanical literature on oplopanax turned up only a single reference to its use in diabetes: one native informant reported that she remembered a white woman taking the plant for diabetes (Thie). Subsequently, it appears that in recent decades use of the plant among natives for diabetes has become common (Thommassen et al.), and it appears from the published studies that the plant benefits patients subjectively in some way unrelated to glycemic control (Justice; Thommassen et al.).

Because oplopanax has no demonstrated action of blood glucose or insulin there is no rationale for using it to treat underlying insulin resistance syndrome.

Brickellia

Brickellia grandiflora (progidiosa) and related species are used in popular medicine in Mexico and the Southwest U.S. to control elevated blood sugar in diabetes (Moore). Research in Mexico suggests that the mechanism is through stimulation of insulin from the pancreas (Peres-Gutierrez). Extracts were given to diabetic and normal mice. As expected, the extract lowered blood sugar in the diabetic mice, but also lowered blood sugar by 40% in the normal mice. An agent acting to normalize insulin resistance would not

be expected to do this, while the result is typical of an agent that either stimulates insulin release or decreases liver release of glucose.

Syzygium

Syzygium jambolana, fructus (*S. cumini*, *Eugenia jambolana* Lam, *Eugenia cumini* Druce, *Myrtus cumini* Linn), common name Jambul, has been used in traditional Egyptian (El Gammel), Unani (Said), and Ayurvedic medicine (Kar et al.; Grover et al. 2001; Rathi) to treat diabetes. The activity has been confirmed in some animal trials (Kar et al.; Grover et al., 2001; Rao and Rao), but not in others. The plant part used may be important. The leaf decoction was found ineffective in diabetic animals (Pepato et al.) and in non-diabetic human volunteers (Teixeira et al. 2000). A tea of the seeds was ineffective in animals (Teixeira et al. 1997). Powders or decoctions of the dried seeds were effective in animals in another trial (Grover et al. 2000). The fruit pulp was effective in another animal trial (Achrekar et al.). Research into the mechanisms of action of *Syzygium* are contradictory, with some animal trials showing an inhibition of the liver enzymes that release blood glucose (Grover et al. 2000) or stimulating insulin secretion (Achrekar et al.), and one trial showed a lowered insulin response to a fructose challenge (Vikrant et al. 2001).

Herbs that may enhance insulin sensitivity

Foeniculum

In a trial of a fenugreek extract (*Foeniculum vulgare*) in twenty-five patients with Type II diabetes, a trial group of thirteen patients received one gram a day of an evaporated hydro-alcoholic extract of fenugreek seeds for two months. At the end of the period, blood sugar responses to a meal were significantly lower in the fenugreek group. Insulin secretion was also lower, as were serum triglycerides (TG). HDL cholesterol was improved, and a standard measure of insulin sensitivity showed increased insulin sensitivity (Gupta et al.).

Dose of powder has varied in different trials from 18 grams (Sowmya and Rajyalakshmi) to 100 grams (Sharma 1990) with several trials giving 25 grams (Sharma, Sarkar et al.). Long term compliance can therefore be difficult. In some clinical trial in India, the powder was mixed into chipati flour for easier compliance. In several trials, an evaporated hydro-alcoholic

extract was effective (Gupta et al.), as was an aqueous extract (Abdel-Barry).

Cinnamomum

Chinese diabetes researchers investigating traditional formulas for diabetes discovered that a formula based on cinnamon and prepared aconite (*quei fu di huang wan*) lowered blood glucose in test animals. The formula suppressed the production of glucose in the liver in a manner similar to that of metformin. They then separately tested the cinnamon and the aconite. Both herbs lowered glucose, the aconite by suppressing gluconeogenesis, and the cinnamon by some other unidentified mechanism (Cheng et al.).

Studies at the U.S. Department of Agriculture suggest that cinnamon acts in some manner to potentiate the action of insulin on the target cell (Berrio et al.; Broadhurst et al.; Khan et al.). Other researchers found that cinnamon components help to activate specific cellular responses to insulin (Imparl-Radosevish et al.; Jarvill-Taylor et al.) thus increasing insulin sensitivity.

Grifola

Maitake mushroom (*Grifola spp.*) has been shown in animals to lower both blood glucose and insulin (Talpur; Manohar; Horio; Kubo). It improves many aspects of hyperinsulinemia, including blood sugar, HBA1C (a measure of long term glycemic control) (Talpur et al.), insulin levels, and triglycerides (Talpur et al.; Kubo et al.). Two case reports have appeared in the literature suggesting that grifola polysaccharides in moderate doses may completely replace conventional antidiabetic drugs (Konno). The animal trials indicate that either the powder of maitake or a water extract may be effective. The mechanism seems only to involve an increase in insulin sensitivity.

Momordica charantia

Momordica charantia (bitter melon) has been in continuous use since antiquity to treat diabetes in Ayurvedic, Unani, and Egyptian medicine (Grover et al. 2002; El Gammel). Many trials have verified its use to lower blood glucose in experimental animals (Kar; Miora; Vikrant), and the property has been confirmed in humans, where the plant lowered blood glucose in 86% of diabetic patients tested (Ahmad). It has also been shown to reduce diabetic pathological endpoints in animals, such as cataract (Rathi) and kidney damage (Grover et al., 2001). It appears to act by increasing insulin sensitivity in the peripheral tissues (Miura et al.).

Momordica prevents both hyperinsulinemia and hypertriglyceridemia (Vikrant et al.).

Ocimum

Various species of basil (*Ocimum* species) have been used in traditional medicine to treat diabetes, including *O. sanctum* (Kar et al.; Grover et al.), *O. canum* (Nyarko et al.), *O. gratissimum* (Aguiyi et al.) and *O. ablum* (Agrawal et al.). A number of trials have demonstrated a hypoglycemic effect in animals (Kar et al.; Nyarko et al.; Vats et al.; Aguiyi et al.; Chattopadhyay; Rai et al.). An anti-hyperglycemic effect has been confirmed on both fasting and post-prandial blood glucose in a human clinical trial (Agrawal et al.). Studies in animals (Chattopadhyay et al.) and humans (Viseshakul et al.) suggest that its action is through increasing insulin sensitivity in the cells.

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