

Nutritional Support for Insulin Resistance: A Summary

BY DAN LUKACZER, N.D.

Blood sugar, or serum glucose, is the basic fuel that all cells in the body use to make energy. Glucose can only be put to work and transformed into energy once it is in the cells, not when it is circulating in the bloodstream. In an optimal state, the body maintains the blood glucose level in a fairly narrow range. Not too low (which is called *hypoglycemia*), and not too high (called *hyperglycemia*). This stability is important because imbalances, particularly raised levels, can cause serious health problems. Chronically elevated blood glucose levels result in the development of diabetes, which can lead to severe complications such as cataracts, blindness, kidney failure, and heart disease.³

The body keeps blood sugar levels in the normal range through the secretion of the hormone, insulin, which allows glucose to be transported from the bloodstream into the cells. However, in many individuals the cells don't respond to the insulin "signal" to allow glucose to exit the blood and enter the cells. The body's response to this is to secrete more insulin. This situation has been called 'insulin resistance' and can be measured in the blood through high serum insulin levels.²⁻⁷

Producing more insulin may be beneficial in the short run because it prevents elevated blood glucose levels. However, the resultant elevated insulin levels (hyperinsulinemia) are considered a significant risk factor for type 2 diabetes, hypertension, and heart disease.⁹ Additionally, elevated insulin may be associated with weight gain and difficulty with weight loss, other blood sugar problems such as hypoglycemia, and some menstrual-related imbalances.⁴¹

What seems to cause this problem of insulin resistance? While genes play a role in predisposing people to this problem, lifestyle has a profound and often overriding influence. The standard American diet of simple sugars, processed foods, and saturated fats must shoulder a portion of the blame, in addition to factors such as obesity, exercise, and smoking.³⁸⁻⁴⁰ Regular exercise, even of moderate intensity, helps lower blood sugar and increases insulin sensitivity; it also helps lower blood pressure, improve cholesterol levels, and decrease body fat.^{36,37}

NUTRITIONAL MODULATION OF INSULIN RESISTANCE

A significant amount of research suggests certain vitamins, minerals, and phytonutrients in foods can improve the sensitivity of the body to insulin. That is, they improve the efficiency of insulin, thus decreasing the amount that the body needs to achieve the same effect.

Glycemic Index—Consuming foods with a low glycemic index (GI) helps to control blood sugar levels and reduce caloric intake.⁶⁹ The GI is defined as the rise in blood sugar following the consumption of a particular food as compared to the rise generated by the ingestion of a standardized test food (usually white bread or glucose). Thus, the lower the GI the less the pancreas needs to work to keep blood sugar levels in the normal range. Studies in both men and women show that diets with a low GI are associated with a lower risk of developing type 2 diabetes and heart disease.^{70,71}

Fiber—Fiber plays an important role in promoting a healthy insulin and blood sugar response. In particular, soluble fibers act favorably on insulin concentrations.^{62,63} Fiber appears to slow digestion, which helps to prevent a surge of blood sugar and resulting insulin response.⁶⁵

Fats—The type of fats that are consumed can play a role in insulin resistance. Saturated fats and trans fatty acids, such as those found in red meats and processed foods, can decrease the fluidity of cell membranes and the binding of insulin to its receptors.⁵¹⁻⁵³ When healthy fats, such as omega-3 essential fatty acids, are substituted into a high fat diet, insulin resistance in skeletal muscle may be prevented.^{54,55} These omega-3 fatty acids, such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), demonstrate a

beneficial effect on insulin and blood sugar by improving the function of insulin receptors and blood sugar transporters in the cell.^{51,52} They may also increase cell membrane fluidity, thus promoting insulin action. Furthermore, EPA and DHA nutritionally support cardiovascular health and help maintain healthy cholesterol and triglyceride levels.

Magnesium—Magnesium plays an important role in maintaining healthy blood sugar levels by altering both insulin secretion and action.⁷⁴ Daily magnesium supplements appear to improve blood sugar transport into the cell. Tissue levels of magnesium are often low in diabetics and even in individuals with normal glucose control.^{74,76,77} Low magnesium results in impairment in insulin action and a worsening of insulin resistance in those with high blood pressure and type 2 diabetes.^{74,78}

Chromium—Much work has been done exploring the relationship between chromium and glucose tolerance.^{80,81} Chromium promotes glucose uptake by the cell and may affect the action of insulin.⁸² Chromium deficiency is associated with elevated blood sugar levels, high cholesterol, and the development of plaque on artery walls.⁸³ Beneficial effects of supplemental chromium on blood lipids such as cholesterol have been reported in controlled trials.⁸⁴ Recent studies have also suggested that chromium can significantly reduce blood sugar levels in type 2 diabetics.^{85,86}

Vanadium—In both animal and human studies, vanadium has demonstrated insulin-like effects on glucose metabolism.⁸⁷ It does not replace insulin, but rather appears to activate cellular insulin receptors, leading to an increase in the transport of glucose into the cell.^{88,89}

Biotin—Biotin deficiency has been suggested to result in an impairment of glucose tolerance. Animal studies suggest that a high biotin intake can improve the utilization of glucose without increased insulin secretion from the pancreas.⁹² High dose biotin has been shown to substantially lower fasting glucose in type 2 diabetic patients.⁹⁴

Conjugated Linoleic Acid (CLA)—CLA is a naturally occurring fatty acid that may support healthy blood sugar and insulin metabolism through its activation of certain signaling agents inside the cell.^{95,96} By enhancing insulin sensitivity of the cells, and therefore blood sugar uptake, CLA may help to promote healthy blood sugar levels and improve hyperinsulinemia.⁹⁸

Alpha-Lipoic Acid (ALA)—ALA is a natural compound that supports blood sugar transport, metabolism, and utilization.⁹⁹⁻¹⁰² Thus, ALA may promote healthy blood sugar clearance from the bloodstream. A recent human trial demonstrated that ALA can improve insulin sensitivity in patients with type 2 diabetes.¹⁰³ ALA also helps protect and maintain the structural integrity of body tissues, such as the eyes, by inhibiting the formation of damaging protein/sugar complexes. Furthermore, ALA provides antioxidant protection and helps improve blood flow to peripheral nerves. A number of trials have shown positive results with ALA in the treatment of diabetic polyneuropathy, a complication of diabetes.¹⁰⁴

Antioxidant Nutrients—An increase in the generation of damaging free radicals and resulting oxidative stress may be associated with insulin resistance.¹⁰⁵ Antioxidants such as vitamins E and C, zinc, and selenium have been shown to protect against free radicals and reduce oxidative stress.¹¹²⁻¹¹⁴ Furthermore, high-dose vitamin E has been reported to significantly increase insulin sensitivity in type 2 diabetics,¹⁰⁹ as well as to improve fasting insulin levels in non-diabetics.¹¹⁰

Herbal Therapies—In addition to the nutrients discussed above, several herbs have been studied for their potential in lowering blood glucose levels. The more promising and better-studied herbs include fenugreek (*Trigonella foenum-graecum*), bitter melon (*Momordica charantia*), and gurmur (*Gymnema sylvestre*).

Nutritional Support for Insulin Resistance

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ABSTRACT: *The binding of insulin to its receptor in the cell membrane is the first step of a metabolic cascade leading to cellular glucose uptake. The term 'insulin resistance' refers to a reduced sensitivity of the cell to the action of insulin. When reduced insulin sensitivity exists, the body attempts to overcome the resistance by secreting increasing amounts of insulin. The development of type 2, or non-insulin dependent, diabetes occurs when the pancreas fails to adequately sustain this increased insulin secretion (hyperinsulinemia). Insulin resistance and hyperinsulinemia are not only significant risk factors for the*

development of type 2 diabetes mellitus, but hypertension, coronary heart disease, and polycystic ovary syndrome as well. Additionally, evidence suggests that breast and colon cancer may be causally related. While genetics may establish propensity, dietary and lifestyle factors are important determinants in the phenotypic expression of this multifactorial disorder that affects at least 25% of the U.S. population. A comprehensive clinical management strategy that incorporates lifestyle and dietary modifications along with nutritional supplement recommendations is essential.

Over 60 years ago Dr. H.P. Himsworth conducted a series of elegant experiments and put forth the then heretical notion that diabetes was not a disease that resulted from a lack of insulin, but rather appeared in the presence of near normal levels of insulin. The defect, or 'essential lesion,' as he saw it, was the diminished ability of the tissues to utilize glucose. He at that time used the term "insulin insensitivity" to describe this observation.¹ It took another 40 years until a consensus was reached on this radical notion. It is now clear that the vast majority of patients with type 2 diabetes show an insulin insensitivity in which they cannot adequately dispose of glucose; and further, that this defect in fact predicts the development of the disease.^{2,3}

ETIOLOGY OF INSULIN RESISTANCE

In most tissues, adequate insulin secretion is necessary for proper glucose disposal and management, since binding of insulin to its receptor in the cell membrane is the first step of a metabolic cascade leading to cellular glucose uptake and metabolism.⁴ Insulin resistance (or as Himsworth termed it, "insensitivity") results when normal insulin action is impaired and the cell does not 'hear' the message of the insulin molecule. To overcome this impairment, and to maintain glucose homeostasis, the pancreas will attempt to secrete larger and larger amounts of insulin.⁵ Without this compensatory hyperinsulinemia, individuals who are insulin resistant develop glucose intolerance and diabetes. If the pancreas can continue to secrete large amounts of insulin the individual then continues to maintain near normal glucose homeostasis.

There is great variation in the general population in the ability of insulin to mediate glucose disposal. Studies have shown that insulin sensitivity can vary up to 10-fold in non-diabetics.⁶ Insulin resistance and the resultant hyperinsulinemia is also surprisingly common, and may be seen in as many as 25% of a nor-

mal non-diabetic population.⁷ Most individuals who develop insulin resistance maintain normal to near normal glucose control, and it is estimated that 60 to 70 million Americans fall into this category. However, up to 25% of these individuals will go on to develop type 2 diabetes, as their compensatory hyperinsulinemia fails and glucose is no longer controlled.

There are an estimated 16 million type 2 diabetics in the U.S. and the overwhelming majority carries the underlying pathophysiology of insulin resistance.⁸ The relative severity of insulin resistance and impairment of pancreatic beta cell function determines the severity of hyperinsulinemia and when *or if* hyperglycemia occurs. Normally, insulin has a suppressive effect on circulating free fatty acids (FFA). When the insulin secretory response declines, circulating FFA levels become elevated. FFAs, in turn, stimulate hepatic glucose production. Without the normal insulin modulatory signal, hyperglycemia occurs as the liver continues to secrete normal amounts of glucose into a greatly expanded plasma glucose pool.⁷ After the onset of type 2 diabetes there is a further reduction in beta cell function (possibly as a result of glucotoxicity) and, eventually, a fall in insulin.

INSULIN RESISTANCE AND CHRONIC DISEASE

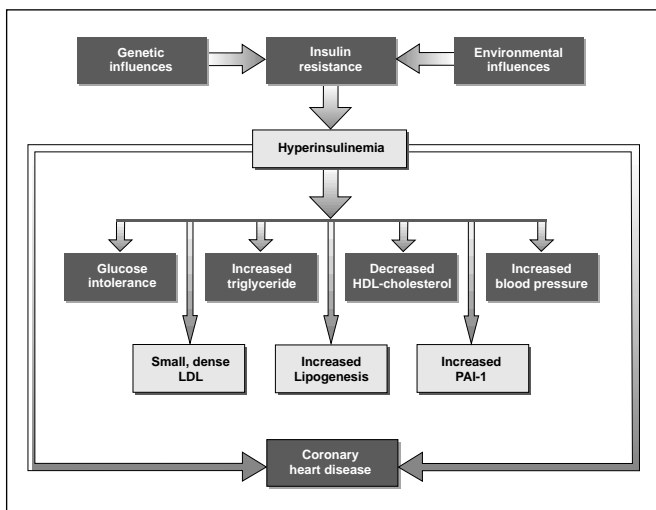
Not all individuals who are insulin resistant ultimately develop diabetes; however, those that do not are at increased risk for hypertension (HBP), stroke, and coronary heart disease (CHD).⁹ The Insulin Resistance Syndrome (IRS), also referred to as Syndrome X or Metabolic Syndrome, refers to a cluster of symptoms characterized by varying degrees of glucose intolerance, abnormal high-density lipoprotein (HDL) cholesterol and/or triglyceride levels, high blood pressure, and upper body obesity, which are all independent risk factors for CHD. The underlying pathophysiology of IRS involves insulin resistance and the consequent hyperinsulinemia. There is now a substantial and

growing body of evidence that supports these relationships, as well as links with polycystic ovarian syndrome (PCOS), and possibly colon and breast cancer.

Coronary Heart Disease

As indicated, those individuals who maintain the compensatory hyperinsulinemia in the face of insulin insensitivity do so at great biological cost. A primary consequence is increased risk for CHD (Figure 1). Insulin resistance may be associated with CHD through three mechanisms: 1.) elevated insulin directly stimulates lipogenesis in arterial tissue and enhances the growth and proliferation of arterial smooth muscle cells, contributing to arteriosclerosis; 2.) insulin resistance and hyperinsulinemia decrease fibrinolysis by stimulating plasminogen activator inhibitor 1 (PAI-1), which is associated with an increased risk for coronary thrombosis. PAI-1 is higher in patients with CHD and is related to insulin resistance and insulin-mediated glucose disposal;^{10,11} and 3.) hyperinsulinemia leads to increased hepatic production of triglycerides (TG) and inhibition of HDL. Elevated TG and depressed HDL are important risk factors for CHD.¹²⁻¹⁴ This strong relationship between insulin, TG, and HDL apparently results from insulin's influence on the cholesteryl ester transfer protein, which promotes the movement of cholesteryl ester from HDL to very low-density lipoproteins (VLDL). The higher the TG levels the greater the losses of cholesteryl ester from HDL and the lower the plasma HDL-cholesterol concentration.¹⁵ Additionally, Apo A1, which is the major protein associated with HDL and independently associated with reduced risk of CHD, is catabolized in a high insulin state, further degrading HDL.

Figure 1. The Link Between Insulin Resistance and Coronary Heart Disease



Insulin resistance may also play a key role in hypertension. As many as 50% of the hypertensive population may be insulin resistant.¹⁶ The sodium hypothesis of hypertension attributes increased peripheral vascular resistance to elevated intracellular sodium concentrations. Based on cross-cultural comparisons, this was thought to be mainly due to increased dietary intake of sodium in salt sensitive individuals. Intraculture studies suggest, however, that dietary salt may account for only a minor segment of increased blood pressure in the hypertensive population. It has been proposed that a larger segment of essential hypertension is caused by enhanced renal sodium reabsorption in the distal tubule promoted by hyperinsulinemia.¹⁷

Hyperinsulinemia may also play a role by altering internal sodium and potassium distribution in a direction that is associated with increased peripheral vascular resistance.¹⁷ Additionally, insulin also appears to work through other mechanisms to increase sympathetic nervous system activity and thus peripheral resistance.¹⁸ This relationship between insulin and blood pressure is further supported by studies that show blood pressure drops when the insulin dose is decreased in obese hypertensive patients with type 2 diabetes.¹⁹ Additionally, blood pressure increases when insulin treatment is initiated in diabetic patients.²⁰

Polycystic Ovary Syndrome

Insulin resistance also appears to have a critical relationship to androgen hormonal modulation. Research over the past 10 years has linked insulin resistance and hyperinsulinemia with PCOS, a prevalent disorder affecting an estimated 6% of women of reproductive age and the most common cause of female infertility in the U.S.²¹ Hirsutism and acne are also common consequences of this disorder. Studies have shown that high circulating insulin may stimulate ovarian cytochrome P450c17 α and 17,20-lyase enzymes in predisposed women, resulting in elevations in serum testosterone and free unbound testosterone, which is associated with the signs and symptoms seen in PCOS.

Insulin influences the androgenic state not only by directly affecting the metabolism of ovarian androgens, but also indirectly by regulating circulation levels of sex hormone binding protein (SHBG). Insulin has been shown to lower the production of SHBG.²² SHBG binds to testosterone and estrogens, making them biologically unavailable. Lowered SHBG therefore indirectly increases the delivery of testosterone to tissues because more testosterone is unbound and bioavailable.²³ Studies indicate that improving insulin sensitivity and decreasing circulating insulin beneficially affects women with PCOS.^{24,25} Of course, every woman who is insulin resistant and hyperinsulinemic does not develop PCOS, suggesting, as with other conditions correlated with IRS, that there is genetic heterogeneity predisposing an individual to respond to the effects of high circulating insulin. Not surprisingly, women with PCOS are also at increased risk for the other metabolic changes associated with IRS.

Cancer

Another area of increasing research interest is the relationship of insulin resistance to cancer. One hypothesis has postulated a link between colorectal cancer, insulin resistance, and hyperinsulinemia.²⁶ While the epidemiological data is not completely consistent, the two largest prospective studies to date do support a modest correlation between colorectal cancer risk and diabetes.^{27,28} Additional support for a promoting effect of insulin on colorectal carcinogenesis has been found in animal models, thereby providing direct evidence for a possible cause-and-effect relationship between hyperinsulinemia and colorectal cancer.^{29,30}

Even more recently, speculation has centered on the link between hyperinsulinemia and breast cancer.³¹ It has been known for some time that exposure of breast tissue to estrogens increases the risk of breast cancer. It is well established that only the fraction of estrogens unbound to SHBG are biologically available to receptors on target cells. As mentioned earlier, insulin inhibits the formation of SHBG. While SHBG binds to both testosterone and estrogen, it binds preferentially to testosterone, so decreased levels of SHBG will result in

increased levels of free unbound estrogen.³² Some epidemiological studies have shown that high plasma levels of unbound estrogen are associated with increased risk of breast cancer, at least among postmenopausal women.^{33,34} Such studies do not prove causation, and clearly these links are still controversial; however, they are suggestive and merit further attention.

MODIFIABLE RISK FACTORS

It appears that at the core of insulin resistance is a defect in cellular sensitivity to insulin. As more light has been shed on this disturbance, it is suggested that direct focus be placed on this underlying metabolic dysregulation.³⁵ Although the cellular disturbance is not completely understood at the biochemical level, modifiable factors such as obesity, exercise, and nutrition appear to play a significant role. While genetic background may determine propensity to the disorder, these modifiable factors should be addressed as part of any comprehensive clinical management strategy.

Exercise has profound beneficial effects on insulin resistance and should be aggressively pursued. Numerous studies support the use of exercise in the management of this condition.^{36,37} Conversely, cigarette smoking plays a role in exacerbating insulin resistance in susceptible individuals.³⁸ Obesity plays a pivotal role as well, especially when concentrated around the abdomen and upper body. Obesity and chronic hyperinsulinemia induced by overeating both stimulate insulin resistance. Therefore, weight loss is of prime importance and has been shown to improve insulin resistance.^{39,40} Insulin resistance also predisposes to increased weight gain and difficulty with weight loss because of its anabolic activity.⁴¹ Longitudinal studies suggest that elevated insulin levels may start in childhood, with fasting hyperinsulinemia serving as a predictor of increased body weight gain and obesity.^{41,42}

Care must be taken not to conclude that all insulin resistant individuals are obese. Other factors are involved, as greater than 50% of individuals with IRS are not obese, and individuals may have normalized insulin levels while still remaining overweight.^{43,44} Apparently, the ability of insulin to stimulate glucose uptake varies widely from person to person, with the degree of obesity only one factor.⁴⁵ Although obesity, smoking, and a sedentary lifestyle increase risk and should be managed aggressively, they are not necessarily an essential attribute of this disease. Evidence points to the use of diet and nutritional supplementation as a primary clinical strategy to manage patients with IRS.

NUTRITIONAL MODULATION OF IRS

In addition to appropriate lifestyle changes, blood glucose and insulin normalization can be promoted through dietary adjustments and the use of select nutritional supplements. The recommended diet for patients with insulin resistance should be individualized, with consideration given to eating habits and other lifestyle factors. Nutritional supplement recommendations are then developed to meet treatment goals and desired outcomes. Monitoring metabolic parameters, including blood glucose, lipids, blood pressure, and body weight, as well as quality of life, is crucial to ensure successful outcomes.

MACRONUTRIENTS

The relative amounts and type of carbohydrate, protein, fat, and fiber are important factors that influence both glycemic and

insulin response. Therefore, they are important considerations in the patient with IRS, yet the dietary prescription remains controversial. The currently recommended high carbohydrate, low fat diet for type 2 diabetics has been shown in some studies to produce adverse lipid and glycemic effects. High carbohydrate diets decrease insulin receptor numbers, probably as a result of the increased insulin cellular contact and resultant receptor down regulation.⁴⁶ Some studies have shown that high-carbohydrate diets increase triglyceride and VLDL cholesterol levels, and elevate insulin and glucose concentrations in type 2 diabetics.^{47,48} Fat in general has been thought to have little insulinogenic effect. However, alterations in membrane lipid composition and membrane fluidity influence important cellular functions. Studies have suggested that there is an altered membrane dynamic in type 2 diabetics as compared to normal controls, which may influence insulin action. If the decreased response to insulin is, in part, the result of a defect in characteristics or functions of the receptor caused by altered membrane fluidity, attending to membrane dynamics becomes an important therapeutic target.⁴⁹

Fat and Essential Fatty Acids—Fatty acids within the phospholipid bilayer help to determine the physicochemical properties of membranes that, in turn, influence cellular functions, including hormone responsiveness. Dietary fat has been shown to determine to a large extent the composition of cell membrane phospholipids. It appears that direct alterations in the fat composition of the cell membrane can induce changes in insulin responsiveness.

The long-chain polyunsaturated fatty acids (PUFAs) can modulate the function of insulin receptors and glucose transporters through their effects on the surrounding lipid environment.⁵⁰ In cultured cells, increasing cell membrane content of PUFAs increases membrane fluidity, insulin binding to receptors, and insulin action.⁵¹ In animal models it has been shown specifically that omega-3 fatty acids such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) have a beneficial effect on plasma insulin and lipid concentrations.⁵² Conversely, saturated fats and trans fatty acids decrease membrane fluidity and decrease binding of insulin to its receptors.⁵¹⁻⁵³ When omega-3 fatty acids are substituted into a high fat diet, insulin resistance in skeletal muscle may be prevented.^{54,55} In human trials, monounsaturated diets appear to mitigate against these adverse changes as well.⁴⁸ For these reasons, the high-monounsaturated fat diet has been proposed as an alternative to the high carbohydrate diet. Studies using a lower carbohydrate, higher monounsaturated and polyunsaturated fat diet results in decreased fasting glucose, insulin, and triglycerides.⁵⁶⁻⁵⁸ Controversy continues, however, as some studies also show improvement in insulin sensitivity when saturated fat is replaced by carbohydrates.⁵⁹

Carbohydrate—Studies in dietary approaches to IRS are inconsistent, which may be explained by the wide range of physiologic effects that equal amounts of different carbohydrates may have. This has resulted in the study of the glycemic index (GI). The concept of GI developed as the result of intensive carbohydrate research that showed that similar amounts of carbohydrate in foods did not elicit similar postprandial glycemic responses.^{60,61} The GI of a food is defined as the blood glucose response to a 50-gram available carbohydrate portion of food expressed as a percentage of the response to the same amount of

Table 1. Nutritional Support Recommendations for Insulin Resistance

Nutrient	Mode of Action	Dosage
Fiber	Beneficial effect on blood glucose control and atherogenic lipoproteins.	30-50 g/day
High-Amylose Starch	Lowers insulin and triglyceride levels, suggesting a beneficial effect on factors involved in insulin sensitivity.	10-20 g/day
Magnesium	Improves the behavior of insulin receptors and improves glucose transport into the cell.	300-800 mg/day
Chromium	Increases cell membrane fluidity and insulin-mediated glucose uptake; lowers fasting and postprandial blood glucose and insulin.	200-1000 mcg/day
Vanadium	Activates cellular insulin receptors, leading to an increase in GLUTs and improved insulin sensitivity.	75-100 mg/day ST* 0.5-2 mg/day LT*
Biotin	Improves the metabolism of glucose without increased insulin secretion.	5-10 mg/day
CLA	Normalizes impaired glucose tolerance and improves hyperinsulinemia by activating PPARs.	1-3 g/day
ALA	Increases insulin-stimulated glucose disposal and improves insulin sensitivity.	600-1800 mg/day
EPA/DHA	Increases cell membrane fluidity, insulin binding to receptors, and insulin action. Beneficial effect on blood lipid concentrations.	1-3 g/day
Vitamin E	Reduces oxidative stress, increases insulin sensitivity, and improves glucose tolerance and fasting insulin levels. Decreases triglyceride and LDL cholesterol levels.	400-1200 IU/day
Zinc	Binds to and stabilizes the insulin molecule, therefore preventing insulin-mediated free radical damage.	15-30 mg/day
Vitamin C	Reduces oxidative stress and improves insulin sensitivity and glucose disposal. Decreases LDL cholesterol and triglyceride levels.	500-1500 mg/day

*ST = short term, LT = long term

carbohydrate from a standard food, which is either glucose or white bread. The GI value depends on a number of factors, such as degree of starch gelatinization, physical form of the food, acidity, food processing, and the presence, amount, and type of protein, fat, fiber, and available carbohydrate in the food. Of these, the effect of fiber and type of starch on glucose response deserve further mention.

It is well known that fiber plays an important role in affecting insulin and glucose response.^{62,63} High fiber, independent of total carbohydrates, has a beneficial effect on blood glucose control and atherogenic lipoproteins.⁶⁴ It appears that soluble fibers in particular act favorably on blood insulin concentrations. Their mode of action appears to be in slowing gastric emptying, and to a lesser extent, inhibition of starch degradation in the upper small intestine.⁶⁵

The type of starch is also an important issue in GI. The starch amylose, as opposed to the more common amylopectin, has a significant positive impact on insulin response in both animal and human studies.^{66,67} Insulin and triglyceride levels were reduced in individuals placed on a high amylose diet, suggesting a beneficial effect on factors involved in insulin sensitivity.⁶⁸ Studies also suggest that a low GI dietary plan helps control blood sugar levels and lead to decreased caloric intake.⁶⁹ Studies in both men and women show that diets with a low GI are associated with a lower risk of developing type 2 diabetes and heart disease.^{70,71} Recently, the United Nations World Health Organization has recommended that all people base their diets on low GI foods.

Protein—Protein may also have an impact on insulin and glucose response. Some studies have shown protein ingestion results in a blunting of the glucose rise and insulin response in normal individuals.⁷² However, more recent work suggests that protein rich foods may vary in their effect, although in general they exhibit a low to modest response.⁷³

MICRONUTRIENTS

Research has shown that many vitamins, minerals, and other nutrients have the potential to improve insulin sensitivity and stabilize blood glucose levels (Table 1). While the mechanism of action for many of these nutrients has been elucidated, for others the precise mechanism remains under investigation. In either case, the use of nutritional supplementation to modify insulin resistance shows great promise.

Magnesium—Magnesium plays an important role in glucose homeostasis by altering both insulin secretion and action. Adequate intracellular magnesium concentrations may therefore allow for improvement of glucose handling.⁷⁴ Daily magnesium supplements appear to improve the behavior of hormone receptors and improve glucose transport into the cell.⁷⁵ Tissue levels of magnesium are often low in diabetics as well as in individuals with normal glucose disposal.^{74,76,77} Low intracellular magnesium results in impairment in insulin action and a worsening of insulin resistance in hypertensives and type 2 diabetics.^{74,78} A low magnesium concentration in non-diabetic subjects has been associated with relative insulin resistance, glucose intolerance, and hyperinsulinemia.⁷⁹

Chromium—Much work has been done on the relationship between chromium and glucose tolerance.^{80,81} Certain lipophilic forms of chromium have been shown to increase membrane fluidity and insulin-mediated glucose uptake in cultured cells and animal models. Chromium may affect the action of insulin by influencing the rate of insulin internalization, which may regulate the synthesis or insertion of insulin receptors into the plasma membrane.⁸² Chromium functions physiologically to promote the insulin responsiveness of skeletal muscle, and probably adipocytes as well. Chromium deficiency is also associated with elevated blood glucose levels, hypercholesterolemia, and the development of aortic plaques.⁸³ Beneficial effects of supplemental chromium on serum lipids have been reported in controlled trials.⁸⁴ Recent studies have examined the use of chromium in type 2 diabetics and suggest that fasting and postprandial blood glucose and insulin, as well as glycated hemoglobin, are significantly reduced with supplementation.^{85,86}

Vanadium—Vanadyl sulfate is a salt of the mineral vanadium. Although vanadium is ubiquitous in the environment, its essentiality in humans has not been established. However, results from deficiency studies are highly suggestive of an essential role for vanadium as a nutrient in humans.⁸⁷ In both animal and human studies, vanadate and vanadyl forms of vanadium have demonstrated insulin-like effects on glucose metabolism.⁸⁷ However, its exact physiological action is not completely under-

stood. It does not replace insulin by its action, but rather appears to activate cellular insulin receptors either by phosphotyrosine phosphorylation or via inhibition of phosphotyrosine phosphatase enzymes.^{88,89} This leads to an increase in glucose transporter proteins (GLUTs) in the plasma membrane, which are essential for the transport of glucose into the cell. In human trials, vanadium has been shown to improve insulin sensitivity in type 2 diabetes at dosages of 100-125 mg/day.^{89,91} However, long-term studies on high dose vanadium have not been performed, so supplementation should be strictly monitored.

Biotin—Biotin is a vitamin that can be synthesized by microflora in the colon. Biotin deficiency has been suggested to result in an impairment of glucose tolerance. Animal studies suggest that a high biotin intake can improve the metabolism and/or utilization of glucose without acceleration of insulin secretion from the pancreas.⁹² Human studies indicate that intravenous biotin may be useful in the management of diabetes.⁹³ Additionally, it was observed that high dose oral biotin (9 mg/day in divided doses) may substantially lower fasting glucose in type 2 diabetic patients.⁹⁴ While the mechanism remains unresolved, it may be due to the enhancement of the biotin dependent enzyme, pyruvate carboxylase, and its effect on utilization of glucose in the citric acid cycle.

Conjugated Linoleic Acid—Conjugated linoleic acid (CLA) is a mixture of isomers of linoleic acid and is found naturally in dairy products and meats. In vitro models using CLA have shown effects on peroxisome proliferators (PP) similar to that seen by the class of oral insulin sensitizing agents known as thiazolidinediones.^{95,96} PP exert their biological responses as the result of activation of a subgroup of nuclear steroid hormone receptors known as peroxisome proliferator-activated receptors (PPARs). PPARs appear to modulate lipid and insulin metabolism through a variety of mechanisms, including regulation of gene expression and an increase in the mobilization and production of GLUTs. The PPAR agonist thiazolidinediones have been shown to decrease circulating glucose levels and also reverse insulin resistance.⁹⁷ CLA has been shown in animal studies to share some functional similarities to these thiazolidinediones, and has further been shown to normalize impaired glucose tolerance and improve hyperinsulinemia.⁹⁸ Therefore, the effects of CLA on glucose tolerance and glucose homeostasis may prove to be an important therapy for the treatment of IRS in humans.

Alpha-Lipoic Acid—Animal and human studies suggest that alpha-lipoic acid (ALA) increases insulin-stimulated glucose disposal. The mechanisms of action may involve improvement of glucose transport, an increase in the number or activation of GLUTs, or an increase in non-oxidative or oxidative glucose disposal.⁹⁹⁻¹⁰² A recent human trial demonstrated that oral administration of ALA (600-1800 mg/day for 4 weeks) can improve insulin sensitivity in patients with type 2 diabetes.¹⁰³

Additionally, a number of trials have also been conducted using ALA in the treatment of diabetic polyneuropathy (DPN) with doses of at least 600 mg per day. Results generally demonstrate that ALA improves this condition and support the assumption that ALA might exert some of its beneficial effects unassociated with glucose disposal. One hypothesis suggests that its effects in DPN are at least partially due to improved microcirculation.¹⁰⁴

EPA/DHA—As discussed previously, omega-3 PUFAs such as EPA and DHA demonstrate a beneficial effect on plasma insulin and lipid concentrations in animals.⁵² In cultured cells, increasing cell membrane content of PUFAs increases membrane fluidity, insulin binding to receptors, and insulin action.⁵¹ When omega-3 fatty acids are substituted into a high fat diet, insulin resistance in skeletal muscle may be prevented.^{54,55}

Antioxidant Nutrients—Hyperinsulinemia can inhibit proper metabolism of fatty acids, promoting the proinflammatory arachidonic acid cascade and resulting in increased free radical generation and oxidant stress.¹⁰⁵ Animal studies have shown an increase in oxidative stress associated with insulin resistance. The mechanism for this increase may be an enhanced plasma protein glycation that occurs even in the absence of hyperglycemia.¹⁰⁶ Although glycation by-products accumulate at a faster than normal rate in patients with diabetes, the same process, albeit slower, takes place in non-diabetics with IRS due to the development of gradual insulin resistance and elevations of circulating glucose associated with aging.¹⁰⁷ Therefore, a role for oxidative stress and nonenzymatic glycation in IRS is likely. One logical treatment strategy is thus the administration of antioxidants.¹⁰⁸

Human clinical trials of high-dose vitamin E supplementation in type 2 diabetics have demonstrated reduced LDL oxidation and oxidative stress.^{108,109} Furthermore, high-dose vitamin E supplementation (900 mg/day for 4 months) significantly increased insulin sensitivity, improved glucose tolerance, and enhanced insulin-stimulated glucose disposal in type 2 diabetics.¹⁰⁹ High-dose vitamin E has also been shown to improve fasting insulin levels in elderly non-diabetics with CHD.¹¹⁰ Vitamin E has been associated with a decrease in triglycerides and LDL concentrations as well.¹¹¹

Zinc, selenium, and vitamin C have been suggested as three other antioxidant nutrients that may also be important in this syndrome.¹¹² Selenium acts as a coenzyme in glutathione peroxidase activity. Zinc is bound to insulin and stabilizes the molecule and therefore may prevent insulin-mediated free radical damage.¹¹³ Vitamin C has also been shown to have beneficial effects on oxidative stress markers, insulin sensitivity, glucose disposal, and blood lipids in type 2 diabetics at a dose of 1000 mg/day for 4 months.¹¹⁴

Herbal Therapies—In addition to the nutritional interventions discussed, several herbs have been studied for their potential to lower blood glucose levels. The more promising and better studied herbs include fenugreek (*Trigonella foenum-graecum*), bitter melon (*Momordica charantia*), and gurmar (*Gymnema sylvestre*). For a more complete discussion of the use of these and other herbs in the management of patients with dysglycemia, please refer to *Herbal Support for Diabetes Management* (CNI608).

CONCLUSION

Insulin Resistance Syndrome is a multifactorial health condition that affects, by conservative estimates, a quarter of the U.S. population. Loss of insulin sensitivity appears to be a slow process, and returning the ability of the cells to optimal functioning may be a gradual process as well. Recognition and treatment of the underlying biochemical defect, loss of insulin sensitivity, and resistance to glucose disposal is of central importance. While genetic background may determine propensity to the disorder,

modifiable factors such as weight, exercise, smoking, diet, and nutrition appear to play a critical role. **A comprehensive strategy of lifestyle and dietary modifications, along with nutrient supplementation, is an important step in clinical management of this disorder.** Our nutritional therapeutic interventions will continue to grow as our knowledge expands.

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