Insulin Resistance:
Lifestyle and Nutritional Interventions

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Abstract

Insulin resistance appears to be a common feature and a possible contributing factor to several frequent health problems, including type 2 diabetes mellitus, polycystic ovary disease, dyslipidemia, hypertension, cardiovascular disease, sleep apnea, certain hormone-sensitive cancers, and obesity. Modifiable factors thought to contribute to insulin resistance include diet, exercise, smoking, and stress. Lifestyle intervention to address these factors appears to be a critical component of any therapeutic approach. The role of nutritional and botanical substances in the management of insulin resistance requires further elaboration; however, available information suggests some substances are capable of positively influencing insulin resistance. Minerals such as magnesium, calcium, potassium, zinc, chromium, and vanadium appear to have associations with insulin resistance or its management. Amino acids, including L-carnitine, taurine, and L-arginine, might also play a role in the reversal of insulin resistance. Other nutrients, including glutathione, coenzyme Q10, and lipoic acid, also appear to have therapeutic potential. Research on herbal medicines for the treatment of insulin resistance is limited; however, silymarin produced positive results in diabetic patients with alcoholic cirrhosis, and *Inula racemosa* potentiated insulin sensitivity in an animal model.
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Introduction

Estimates suggest that in Westernized countries 25-35 percent of the population have a degree of insulin resistance and the health consequences associated with this metabolic derangement.[1] Insulin resistance means, in its simplest sense, that the ability of insulin to dispose of glucose in the liver, skeletal muscle, and other peripheral tissues is compromised. From a quantitative standpoint, skeletal muscle is presumed to have the greatest impact on whole-body glucose disposal, and hence on insulin resistance. Insulin resistance is usually characterized by higher fasting and post-glucose loading insulin levels, and a decreased responsiveness of tissue to the insulin driven clearance of this glucose from the bloodstream.

Insulin resistance seems to be a common feature and a possible contributing factor to several frequent health problems, including type 2 diabetes mellitus,[2] polycystic ovary disease,[3-5] dyslipidemia,[6] hypertension,[7-8] cardiovascular disease,[9-13] sleep apnea,[14] certain hormone-sensitive cancers,[2,15,16] and obesity.[17-20]

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Table 1: Some Metabolic Associations with Insulin Resistance

- Leptin resistance[23, 24]
- Dyslipidemia[6]
- Elevated lipoprotein(a) levels[25]
- Elevated homocysteine[25]
- High triglycerides[26]
- Impaired glucose transport system of skeletal muscle (GLUT-4)[1]
- Hypercortisolism[27]
- Decreased DHEA[28]
- Low growth hormone levels[29]
- Increased lipogenesis (production of fat) and decreased beta oxidation (burning of fat)[30,31]
- Increased TNFα[32]
- Hemostatic dysfunction including increased thrombosis, high fibrinogen levels, and tendency to platelet aggregation[33]
- Increased blood pressure[7,8]
- Increased oxidative stress[34]

Obesity appears to be predictably accompanied by insulin resistance, with the degree of insulin resistance often in direct proportion to the amount of visceral body fat. This relationship holds across age and sex boundaries.[18,21] Although obesity correlates with insulin resistance, it appears the distribution of body fat might be an even more specific marker. Central or abdominal obesity has been reported to have such a close association with insulin resistance that it is often now viewed as a clinical marker for this metabolic dysregulation.[17] Because of the relationship between central adiposity and insulin resistance and because of the correlation between insulin resistance and increased cardiovascular disease risk, it has been suggested that health care providers should begin using waist measurements as a public health tool in screening for high-risk candidates for cardiovascular disease.[22]

A clustering of metabolic problems associated with insulin resistance, including elevated plasma glucose, lipid regulation problems (elevated triglycerides, increased small low-density lipoproteins, and decreased high-density lipoproteins), high blood pressure, a prothrombic state, and obesity (especially central obesity) occurs commonly together. (Table 1) This combination is referred to as either "The Metabolic Syndrome" or "Syndrome X." Research suggests this cluster of metabolic disorders seems to interact to promote the development of type 2 diabetes, atherosclerosis, and cardiovascular disease. And, while insulin resistance might lie at the heart of the problem, all of these metabolic disorders appear to be closely related and can, together or independently, contribute to health problems.[6,17] Many overweight individuals have either components of or the entire cluster of symptoms associated with this syndrome.[21]

Lifestyle Modifications and Insulin Resistance

The stark reality is that a majority of people with this metabolic problem developed insulin resistance as a result of a lifetime of cumulative poor choices. Factors thought to contribute to insulin resistance include diet, exercise, smoking, and stress. Although there are certainly genetic factors contributing to this metabolic state, since the above factors are all modifiable to a greater or lesser degree, insulin resistance is potentially preventable. Even among those members of the population with a genetic propensity for this metabolic challenge, it appears appropriate lifestyle choices play a large part in its manifestation and reversal.

Diet

The ideal diet for modifying insulin resistance should reduce body weight, decrease fat while sparing muscle tissue, and improve insulin sensitivity. While it is relatively simple to find agreement within the literature on these general points, agreement on the design of an ideal diet to accomplish these goals is far from universal. Some of the factors to consider when designing a diet for an individual with insulin resistance include age, underlying disease or metabolic conditions, activity level, vegetable content of the diet, and types of dietary fat and carbohydrates consumed. Epidemiological evidence suggests increased consumption of saturated and total fat and decreased intake of fiber are associated with insulin resistance as well.[35-37]

Research is also supportive of the benefits of diets high in certain types of fiber for promoting improved post-prandial glucose and insulin responses in normal individuals and in individuals with type 2 diabetes, dyslipidemia, and insulin resistance. The types of dietary fiber that appear to be most significant with respect to insulin resistance include oat fiber and guar gum, while psyllium has produced mixed results.[38-48]

Guar gum has received the most attention as an intervention aimed at managing insulin resistance. While evidence is quite supportive of the potential for this fiber, added to test meals, to contribute to significant reductions in post-prandial glucose and insulin responses,[45] its effect on long-term improvement in insulin resistance is equivocal and might vary among patient populations.

Landin et al conducted a double-blind, placebo-controlled trial to test the effect of guar gum on insulin sensitivity. Twenty-five healthy, non-obese, middle-aged men were given either 10 grams of guar gum or an equivalent dose of a placebo three times daily for six weeks. The findings indicated that in this population guar gum was capable of decreasing fasting blood glucose and improving insulin sensitivity; however, fasting plasma insulin levels were unchanged. Other metabolic parameters, all of which decreased by the administration of guar gum in this trial, included cholesterol, triglycerides, and systolic blood pressure.[46]

Tagliaferro et al investigated the use of guar gum as an addition to a diabetic diet in order to evaluate its impact on blood sugar parameters. They provided four grams of guar gum twice daily to 10 type 2 diabetic subjects. At the end of the treatment period they reported a decrease in fasting insulin levels and a decrease in insulin resistance.[47]

Unfortunately, in the only study that provided guar gum to obese individuals (obesity defined as greater than 50-percent overweight), no improvement in insulin resistance was noted. In this study, Cavallo-Perin et al administered four grams of guar gum twice daily to nine obese individuals for six weeks. Six individuals subsequently had their dose increased to eight grams twice daily for a three-month interval. Based on before and after evaluations, guar gum added to the diet was unable to significantly alter fasting glucose, glucose utilization, or insulin sensitivity.[48]

While high fiber diets seems to be prudent, simply advocating low-fat diets might not be the best suggestion for all insulin resistant subjects. Research indicates the type of fat consumed might be an important consideration. While available information suggests a diet lower in saturated fats might be an advantage, evidence also suggests diets rich in monounsaturated fats might be of benefit, particularly for type 2 diabetic people with insulin resistance.

A diet higher in monounsaturated fat appeared to provide an advantage over a fiber-rich, high-carbohydrate, low-fat diet on body fat distribution among type 2 diabetic subjects. The diet higher in monounsaturated fat generated proportional body fat loss from both upper and lower body. In contrast, the

fiber-rich, high-carbohydrate, low-fat diet resulted in a disproportionate loss of lower-body fat, worsening the ratio between upper and lower body fat distribution.[49] Since evidence supports the association between obesity, abdominal body fat distribution, and insulin resistance, and because among obese men loss of weight and a decrease in the waist-hip ratio are closely associated with improved insulin sensitivity,[50] the diet higher in monounsaturated fat seems to have produced a more favorable impact on metabolism.

Parillo et al randomly assigned 10 people with type 2 diabetes to a 15-day period of either a high-monounsaturated/low-fat diet (40-percent carbohydrate, 40-percent fat, 20-percent protein, and 24 grams of fiber) or a low-monounsaturated/high-carbohydrate diet (60-percent carbohydrate, 20-percent fat, 20-percent protein, and 24 grams of fiber). Their results suggested the high-monounsaturated/low-carbohydrate diet had a more significant impact on improving insulin sensitivity.[51]

Garg et al studied the effects of two isocaloric diets on insulin sensitivity in subjects with type 2 diabetes. All subjects were randomly assigned to receive either a high carbohydrate diet (60 percent of calories from carbohydrate) or a low-carbohydrate diet (35 percent of calories from carbohydrate) for 21 days, and then crossed over to the other diet for an additional 21 days. Both diets were matched for fiber content (25 g/d) and were low in saturated fatty acids. The low-carbohydrate diet was rich in monounsaturated fatty acids. Mean peripheral insulin-mediated glucose disposal was slightly higher on the diet with lower carbohydrate and higher monounsaturated fatty acid content.[52] It appears that for some, if not all, subjects with insulin resistance, a suggestion to follow a low-fat/high-carbohydrate diet, even if this is a high-fiber diet, should be weighed against the cost of sacrificing monounsaturated fats.

Some research has called into question the wisdom of recommending low-fat, high-carbohydrate diets.[53-55] Evidence suggests the macronutrient composition of the diet might play an important role in fat deposition,[56] and so might consequently influence insulin resistance. Several authors, after reviewing available scientific evidence, have suggested that low fat, high carbohydrate diets might contribute to metabolic problems, and certainly do not appear to be capable of reversing insulin resistance, obesity, or Syndrome X.[57,58]

While it is difficult to specify an exact percentage of the diet that should be comprised of carbohydrates, research suggests a diet containing excessive amounts of carbohydrates may contribute to insulin resistance. Similarly, evidence suggests that lowering the percent of the diet consisting of carbohydrates can reverse insulin resistance and positively impact the metabolic profile associated with insulin resistance to some degree. Further complicating the issue of an appropriate percent of carbohydrates to consume might be factors such as the form of the carbohydrates (simple versus complex), health of the subject, age of the subject, fiber content of the diet, other types and quantities of macronutrients consumed, and physical activity levels.

High-carbohydrate, high-fiber diets certainly appear to improve peripheral tissue insulin sensitivity in healthy young and old individuals.[59,60] However, this is often not the population of insulin resistant subjects most in need of dietary intervention. Among insulin resistant subjects with type 2 diabetes and obesity, similar results might not be the norm.

Hoffman et al studied the short-term effects of modifying the diet in favor of a high-fiber/high-carbohydrate diet (81 grams of fiber and 68 percent of calories from carbohydrates) in seven very obese subjects with type 2 diabetes. Pre-intervention baseline diets consisted of 28 grams of fiber and 42-percent carbohydrates. As a control group, five non-obese subjects without diabetes were observed. Reported results suggest this dietary modification was unable to decrease insulin resistance

in this patient population.[61]

Golay et al compared the effects of two low-calorie diets of similar caloric value, but differing in carbohydrate content (25 percent versus 45 percent of calories from carbohydrates) for twelve weeks. Although both diets resulted in improvement, the fasting blood insulin decreased more markedly with the 25-percent carbohydrate diet compared to the 45-percent carbohydrate diet. The researchers also found a slightly greater degree of average weight loss (10.2 kg with the 25-percent carbohydrate diet versus 8.6 kg with the 45-percent carbohydrate diet), and adipose tissue loss (8.1 kg with the 25-percent carbohydrate diet versus 7.1 kg with the 45-percent carbohydrate diet) among individuals following the lower carbohydrate diet. However, the lower carbohydrate diet also resulted in a greater average loss of lean body mass (2.2 kg with the 25-percent carbohydrate diet versus 1.4 kg with the 45-percent carbohydrate diet).[62] Loss of muscle tissue might not be metabolically desirable when trying to decrease insulin resistance, making the accelerated loss of lean muscle mass observed with the lower carbohydrate diet a potential concern.

As an example of the power of varying the relative amounts of macronutrients (in this study proteins and carbohydrates) in a weight loss diet, Skov et al held fat constant at 30 percent of calories, and placed individuals on either a diet consisting of 12-percent protein and 58-percent carbohydrates, or 25-percent protein and 45-percent carbohydrates. The trial lasted six months and the researchers reported that weight loss was almost double in the higher protein diet (8.9 kg verse 5.1 kg). They also found fat loss was higher in the higher protein group (7.6 kg versus 4.3 kg), and that the higher protein diet had a much more substantial ability to reduce triglycerides.[63] The researchers did not monitor insulin resistance, although the higher protein diet generated more positive metabolic changes in areas associated with insulin resistance.

Piatti et al also conducted a weight loss trial. They held the percent of calories from fat constant and modified the relative percent of calories from protein and carbohydrates. The two diets the researchers utilized in this study had the following composition: 45-percent protein, 35-percent carbohydrate, and 20-percent fat; or 20-percent protein, 60-percent carbohydrate, and 20-percent fat. Although diet modifications only lasted 21 days and both diets induced a similar decrease in body weight and fat mass, the higher carbohydrate diet resulted in a greater loss in lean body mass.[64] Since it is not desirable to lose muscle tissue when trying to correct insulin resistance, this evidence suggests a higher protein diet might be the more preferable alternative.

There is also evidence that the amount and range of carotenoid-like pigments in an individual's blood is inversely related to fasting serum insulin levels,[65] suggesting a diet low in vegetables might contribute to insulin resistance. Epidemiological evidence does not support a role of dietary vitamins E or C consumption having a significant association with insulin sensitivity;[66,67] Diets higher in vitamin A, on the other hand, have shown an inverse relationship with insulin resistance.[67] Dietary micronutrient deficiencies might also promote insulin resistance. Chief among these deficiencies appear to be minerals including calcium, magnesium, potassium, chromium, vanadium, and zinc.[68-74]

Intake of sodium, either too high or two low, appears to negatively impact insulin sensitivity. Evidence presented by Donovan et al is suggestive of high sodium intake possibly exacerbating insulin resistance.[75] At the other extreme, salt restriction also appears to increase insulin resistance for most individuals. While moderate dietary sodium reduction may lower blood pressure without a distinct adverse effect on glucose metabolism in subjects with primary hypertension,[76] it appears that salt restriction does not improve insulin resistance in hypertensive subjects.[77] In fact, available

evidence seems to be in agreement that severe reduction of salt intake may contribute to an increased serum lipid and insulin levels, and a deterioration of insulin sensitivity in both healthy volunteers and patients with hypertension.[76,78,79] Evidence even suggests moderate salt restriction can aggravate both existing systemic and vascular insulin resistance.[79]

Cigarette Smoking and Use of Nicotine-Containing Products

Researchers found chronic cigarette smokers were likely to be insulin resistant, hyperinsulinemic, and dyslipidemic when compared with matched groups of non-smokers.[80] A further study demonstrated chronic cigarette smoking markedly aggravated insulin resistance in patients with type 2 diabetes.[81] While abstaining from nicotine completely has been found to appear to improve insulin resistance, smoking cessation methods which rely on other forms of nicotine replacement appear to decrease insulin sensitivity. In order to determine the effect of nicotine-containing chewing gum, Eliasson et al compared insulin sensitivity in 20 healthy, non-obese, middle-aged men who were long-term users to 20 matched-control subjects who did not use nicotine. Their findings suggested the long-term use of nicotine-containing chewing gum was associated with insulin resistance, and the degree of insulin resistance was correlated to the extent of nicotine used.[82] Assali et al also reported that nicotine replacement therapy resulted in a decrease in insulin sensitivity.[83]

Exercise

Exercise may be the single most important lifestyle factor for both preventing and reversing insulin resistance. Kelley and Goodpaster, after reviewing currently published clinical trial data, concluded that physical activity can reduce insulin resistance and improve glucose intolerance among obese individuals.[31] Ivy came to a similar conclusion about the positive benefits of exercise training on insulin resistance among individuals with type 2 diabetes.[84] Lehmann et al also reported regular physical exercise resulted in a significant amelioration of cardiovascular risk factors, including insulin resistance, associated with Syndrome X and diabetes.[85]

Among its many benefits, exercise, independent of changes in energy intake, body composition, and exercise-induced fat burning, actually increases the rate and amount of fat oxidation while at rest.[86] Exercise training results in a preferential loss of abdominal body fat[85] and reverses the loss of muscle mass associated with insulin resistance, providing the single-most important intervention for changes in body composition.[85,87] Exercise improves insulin sensitivity in skeletal muscles and fat tissue, reducing both fasting blood sugar and insulin levels.[87] Findings demonstrate that consistent exercise training, even without accompanying improvements in body composition, improve peripheral insulin activity in subjects with impaired glucose tolerance.[88] A study also demonstrated the skeletal muscle glycogen transport system improved substantially with exercise.[88]

Even an exercise routine as simple as incorporating brisk walking four times weekly dramatically improves endurance fitness, decreases body fat stores, tends to reduce food consumption, and decreases insulin resistance.[89,90] Based on available evidence it is likely an optimal program for improving insulin sensitivity might, in addition to an aerobic component like walking, aim even more specifically to selectively deplete body fat while maintaining or building lean tissue by incorporating resistance training.[91-93]

The benefits of exercise on insulin resistance appears to hold consistently across all age groups and both sexes. In a study of obese children, Ferguson et al demonstrated that four months of exercise training improved insulin resistance and other metabolic factors associated with Syndrome X. These benefits were

Table 2: Some Possible Lifestyle Contributors to Insulin Resistance

- High fat diet
- Very low fat diet
- Low protein diet
- Deficiency of essential fatty acids, especially omega 3 oils as found in fish
- High carbohydrate diet
- High glycemic meals
- Refined sugars and starches
- Excessively high or low salt intake
- Low fiber intake
- Micronutrient deficiencies (such as calcium, magnesium, chromium, vanadium, zinc, carotenoids, and vitamin A)
- Low intake of vegetables
- Lack of exercise or sedentary lifestyle
- High stress
- Use of nicotine-containing products

subsequently lost when the children became less active.[94] Research is in agreement that there is no age limit to extracting the insulin sensitizing effects of exercise among men.[87,92,95] Available research also demonstrates that postmenopausal women can improve insulin resistance through consistent appropriate exercise.[91]

Although exercise is a critical intervention to address insulin resistance, the combination of dietary modifications with exercise is probably an even more effective strategy. While studies on the combined effects of diet and exercise with respect to insulin resistance are unavailable, evidence has demonstrated the combination is much more effective at promoting weight loss than either intervention alone.[1,96-98]

Stress

While the role of stress in the development of insulin resistance is still equivocal, it appears that stress and the physiological response to stress is a hurdle that might interfere with efforts to improve insulin sensitivity. Acute stress is clearly associated with a severe, yet reversible, form of insulin resistance.[99] Raikkonen et al, after studying psychosocial stress and insulin resistance, concluded that stress should be considered in any attempt to understand the pathogenesis of insulin resistance.[100] Nilsson et al similarly found psychosocial stress might be associated with insulin resistance.[101]

While researchers speculate that glucocorticoids, such as the stress hormone cortisol, might contribute to insulin resistance because of their tendency to oppose the actions of insulin,[102] the nature of cortisol's impact on insulin resistance is unclear. From a physiological perspective, both cortisol and the catecholamine stress hormones are capable of elevating blood sugar, and Goldstein et al reported that chronic elevation of cortisol resulted in increased plasma insulin levels.[103] Evidence also suggests that consistently elevated levels of cortisol greatly inhibit nonhepatic glucose utilization (the ability of muscle tissue, for example, to use glucose for energy).[103,104]

Leptin is a hormone secreted by adipose tissue. Higher leptin levels appear to act on the hypothalamus to decrease body fat, increase thermogenesis, and promote satiety. However, evidence indicates that, as the percent of body fat increases, even high levels of leptin are unable to adequately stimulate these metabolic responses, suggesting that obesity is commonly characterized by a state of leptin resistance.[105] Evidence also suggests the amount of leptin found in the blood directly correlates with insulin levels and with insulin resistance. In effect, leptin levels decrease in parallel with insulin, and leptin resistance decreases as a person becomes more sensitive to

insulin.[23,24,106] While more research is needed to clarify the exact nature of the relationship between insulin resistance and leptin resistance, these two metabolic disturbances consistently appear together.

Stress, secondary to cortisol production, also may impact insulin resistance directly or indirectly through interaction with leptin. In animals, evidence suggest cortisol is a primary factor in preventing leptin from increasing thermogenesis and decreasing appetite and body fat. In humans, it appears that cortisol impacts leptin and its activity as well. While more research is required, available evidence indicates cortisol might be capable of both increasing leptin levels and inhibiting the action of leptin, thereby promoting a state of leptin resistance.[107-109] See Table 2 for a summary of lifestyle contributions to insulin resistance.

Nutritional Interventions: Supplementation

The role of nutritional and botanical substances in the management of insulin resistance requires further elaboration; however, available information suggests some substances positively influence insulin resistance. Minerals, including magnesium, calcium, potassium, zinc, chromium, and vanadium, appear to have associations with insulin resistance or its management. Amino acids, including L-carnitine, taurine, and L-arginine, also might play a role in the reversal of insulin resistance. Additional nutrients such as glutathione, coenzyme Q10, and lipoic acid appear to have therapeutic potential. Research on herbal medicines for the treatment of insulin resistance is limited; however, silymarin produced positive results in diabetic patients with alcoholic cirrhosis, and *Inula racemosa* appears to potentiate insulin sensitivity in an animal model.

Minerals

Magnesium

Available research suggests an association between magnesium deficiency and insulin resistance. In two patient populations normally associated with insulin resistance, overweight and type 2 diabetic individuals, magnesium deficiency is a relatively common occurrence.[69,70] Depletion of intracellular free magnesium has also been found to be a characteristic feature of insulin resistance among subjects with essential hypertension.[110]

Nadler et al reported a decrease in insulin sensitivity with magnesium deficiency in all subjects studied.[111] Humphries et al reported a clear association between the lowest consumption of dietary magnesium and the highest degree of insulin resistance among non-diabetic subjects.[112] Dominguez et al confirmed this observation, finding that among both normotensive and hypertensive subjects, a higher magnesium level corresponded to a greater degree of sensitivity to insulin.[110] Looking at this association from another perspective, research indicated an infusion of insulin lowered the ability to accumulate intracellular magnesium, and this response to insulin might be even more exaggerated among individuals with higher degrees of insulin resistance.[113] Lefebvre et al, in their evaluation of magnesium's role in glucose metabolism, concluded, "...magnesium deficiency results in impaired insulin secretion while magnesium replacement restores insulin secretion. Furthermore, experimental magnesium deficiency reduces tissue sensitivity to insulin."[114]

In efforts to clarify the relationship between insulin resistance and magnesium, several research groups have examined the effects of magnesium supplementation and glucose handling. Paolisso et al conducted a double-blind, randomized, crossover study to test the impact of magnesium supplementation on, among other factors, insulin resistance in elderly individuals. They provided subjects with 4.5 grams magnesium daily for four

weeks, which resulted in a significant increase in erythrocyte magnesium concentrations. This intervention also resulted in an improvement in insulin sensitivity, and this improvement correlated with the improved magnesium status.[115] Unfortunately, similar improvements in glucose control were not found in a study of magnesium supplementation in people with type 2 diabetes. While Eibl et al showed that oral magnesium supplementation (30 mmol/day) for three months resulted in a significant improvement in plasma magnesium levels, this improvement was not sustained following discontinuation of magnesium, and no significant changes in the metabolic control of blood sugar were observed.[116]

Calcium

While information on calcium supplementation and insulin resistance is limited, it appears, at least in some patient populations, administration of calcium might generate positive outcomes. Sanchez et al investigated the impact of calcium supplementation on insulin resistance in 20 non-diabetic, hypertensive subjects. All subjects were placed on standardized diets consisting of approximately 500 mg dietary calcium per day for four weeks. Following this period, 1500 mg either calcium or placebo were given daily in a randomized, double-blind fashion for eight weeks. Following the intervention period, treated patients had decreased fasting plasma insulin levels and a significant increase in insulin sensitivity.[68]

Potassium

A potassium-depleted diet was found to lead to insulin resistance at post-receptor sites, a resistance that was reversed when potassium was resupplied.[71] Currently, no information is available on potassium supplementation under other circumstances; however, this mineral appears to have a close association with insulin resistance and merits future investigation.

Zinc

Preliminary evidence suggests a relationship between zinc deficiency and the response to insulin. In human subjects, information contained in an abstract of an untranslated Japanese research article implied a clinical correlation between low zinc levels and insulin resistance.[74] The prevalence of several of the diseases or metabolic dysfunctions associated with insulin resistance are also much more common among individuals consuming low zinc diets (Table 3).[117]

Table 3: Conditions Associated with both Low Zinc Diets and Insulin Resistance

Cardiovascular Disease
Type 2 diabetes
Hypertension
Dyslipidemia
Hypertriglyceridemia
Impaired Glucose Tolerance

Chromium

Animal experiments have shown that a deficiency in chromium can result in insulin resistance.[118,119] Evidence also suggests diet-induced insulin resistance in experimental animals can be improved by chromium.[120] In humans, there also seems to be an association between insulin resistance and chromium status.[121]

Morris et al suggested a compromised ability to retain chromium by individuals with type 2 diabetes might contribute to the insulin resistance found in this population. Compared with healthy controls, these researchers found 33-percent lower mean plasma levels of chromium and 100-percent higher urine values, suggesting a disruption in the ability to sustain appropriate chromium status.[122] Morris et

al demonstrated a reduction in fasting plasma chromium levels and an increase in urinary elimination of chromium followed an infusion of glucose and the resultant insulin surge in healthy individuals. Based on their experiments, it appeared the elevated insulin levels were impacting chromium status.[123] Evidence also suggests that individuals consuming diets with the lowest amounts of chromium tend to have disruptions in glucose and insulin regulation.[72]

While available evidence seems to clearly indicate a role for chromium in glucose metabolism, and an interaction between chromium status and insulin resistance, chromium's therapeutic role is equivocal. Several forms of chromium have been studied with respect to glucose metabolism; however, studies of chromium supplementation and its impact on insulin resistance are much more limited. Controversy exists as to which supplemental form of chromium is preferable; and, regarding insulin resistance this controversy is likely to continue until well-designed comparative studies are conducted in humans.

Chromium complexed with nicotinic acid appeared to have a modest effect on glucose metabolism in subjects with type 2 diabetes.[124] However, this form of chromium has yet to be specifically studied regarding insulin resistance in humans. Similarly, glucose tolerance factor (GTF) chromium-rich brewer's yeast has yet to be studied with respect to insulin resistance, but has been shown to impact some aspects of glucose metabolism in elderly subjects.[125] Chromium chloride appears to influence glucose and insulin levels in healthy adult men with evidence of insulin resistance in a manner suggestive of an improvement in insulin sensitivity.[126]

Chromium picolinate also appears to have the potential to positively influence insulin resistance under some circumstances. Anderson et al reported a chromium-induced improvement in both glucose tolerance and circulating insulin among non-diabetic individuals with moderate post-glucose challenge hyperglycemia. The experimental group received 200 mcg chromium picolinate daily. Observed changes in glucose and insulin levels following the intervention period were suggestive of increased tissue sensitivity to insulin.[127]

Anderson et al also investigated the effect of chromium picolinate supplementation as a sole intervention on parameters of glucose metabolism among type 2 diabetic patients. One hundred and eighty men and women were randomly assigned to groups receiving either a placebo, 100 mcg chromium picolinate twice daily, or 500 mcg chromium picolinate twice daily. During the trial, subjects continued all medications and were instructed to sustain their normal eating and lifestyle habits. Fasting glucose, two-hour glucose levels, and fasting and 2-hour insulin values decreased significantly during the four-month study in both groups receiving the supplementary chromium, suggestive of an improvement in insulin resistance.[128]

However, not all studies on chromium picolinate administration and its impact on glucose and insulin response have yielded positive results. Lee et al conducted a prospective, double-blind, placebo-controlled, crossover study to determine the effect of chromium picolinate on individuals with type 2 diabetes. Although triglycerides were improved, no statistical difference was noted between control and chromium-treated subjects with respect to measured parameters of glucose control at the conclusion of this six-month study.[129] Although these researchers did not measure insulin resistance, the lack of effect on measured parameters suggests it is unlikely tissue sensitivity to insulin was dramatically altered.

Joseph et al found no added benefit of chromium picolinate supplementation when it was provided in addition to resistance training. In this study, 32 moderately overweight men and women were observed in order to determine the effect of 12 weeks of resistance

training on parameters of glucose metabolism, with or without chromium picolinate supplementation (924 mcg per day). Their results suggested the expected resistance training enhancement of insulin sensitivity; however, the subjects with and without chromium picolinate had no significant difference in any parameter measured,[130] suggesting any effect chromium picolinate supplementation might have on insulin resistance is either inconsequential in combination with or vanishes with resistance training.

Vanadyl Sulfate

Vanadium, as vanadyl sulfate, is a trace mineral associated with sugar regulation. It is believed to regulate fasting blood sugar levels and improve receptor sensitivity to insulin.[73] Based on available research, vanadyl sulfate appears to be a useful intervention for type 2 diabetic individuals with insulin resistance.

Boden et al conducted a single-blind, placebo-controlled study of the effect of vanadyl sulfate on eight male and female subjects with type 2 diabetes. Treated subjects received 50 mg vanadyl sulfate twice daily for four weeks, followed by a four-week placebo phase. Modest improvements in fasting glucose and hepatic insulin resistance followed the treatment period and were sustained throughout the placebo period.[73]

Halberstam et al provided 100 mg vanadyl sulfate daily for three weeks to moderately obese type 2 diabetic and non-diabetic subjects. They observed a decrease in fasting plasma glucose and a significant improvement in insulin sensitivity in the type 2 diabetic subjects; however, no change was observed in the obese non-diabetic subjects. The authors concluded that at this dose vanadyl sulfate was capable of improving insulin sensitivity in type 2 diabetic subjects but was unable to alter insulin sensitivity among obese, non-diabetics.[131]

Cohen et al also examined the effect of vanadyl sulfate (100 mg per day) in type 2 diabetes following a three-week intervention period. Measurement of fasting plasma glucose and insulin-mediated glucose disposal during pre- and post-treatment periods suggested a beneficial effect of vanadyl sulfate on improving both hepatic and peripheral insulin sensitivity. These effects were sustained for up to two weeks after the vanady sulfate was discontinued.[132]

Vitamins

Biotin

In experimental models of type 2 diabetes, biotin lowered post-prandial glucose levels, improved insulin response to a glucose load, and decreased insulin resistance.[133] Although biotin has not been evaluated in humans for its effect on insulin resistance, this vitamin has demonstrated an ability to improve glucose metabolism in humans on dialysis and with type 2 diabetes,[134] thus warranting future investigation.

Vitamin E

Clinical studies on vitamin E in insulin sensitivity have been conflicting. In a somewhat surprising finding, Skrha et al reported supplementation with vitamin E might actually worsen insulin status in some patient populations. Vitamin E (600 mg daily) was given for three months to 11 obese individuals with type 2 diabetes. They found that vitamin E resulted in a decrease in both glucose disposal rate and number of insulin receptors on erythrocytes.[135] However, Barbagallo et al reported an improvement in insulin sensitivity among hypertensive patients following a four-week double-blind, randomized study of vitamin E administration (600 mg/d). The results demonstrated a significant improvement in whole-body glucose disposal subsequent to vitamin E treatment.[136]

Amino Acids

L-Carnitine

Administration of L-carnitine holds potential to improve insulin sensitivity. In a study evaluating the effect of parenteral administration of L-carnitine (either two or four grams per day) on metabolic parameters subsequent to post surgical-stress, Heller et al concluded that carnitine administration was capable of reducing the associated trend toward insulin resistance.[137] Gunal et al also reported a single intravenous dose of L-carnitine (one gram) had a positive effect on insulin sensitivity in patients with chronic renal failure.[138] Mingrone et al found a two-hour infusion of L-carnitine administered to patients with type 2 diabetes created at least a short-term improvement in insulin sensitivity by enhancing whole-body glucose uptake and increasing glucose storage. They observed a similar positive metabolic effect in normal subjects.[139]

Taurine

The effectiveness of taurine supplementation on human cases of insulin resistance has yet to be documented; however, preliminary experimental evidence from animal models is intriguing. Anuradha et al reported that adding taurine to the diet of fructose-fed rats moderated the fructose-induced exaggerated glucose levels and hyperinsulinemia.[140] Nakaya et al noted a similar positive effect of taurine on insulin sensitivity in a rat model of type 2 diabetes. In this study, administration of taurine resulted in significantly less abdominal fat accumulation, hyperglycemia, and insulin resistance.[141] While it is impossible to extrapolate these results to human subjects, this research does suggest taurine is a nutritional intervention that merits further investigation.

L-Arginine

Although additional research is required, arginine is another amino acid with a potential therapeutic role in the management of insulin resistance. In children with thalassemia major, serum insulin concentrations were significantly lower 30 minutes after arginine infusion. Conversely, arginine-stimulated glucagon secretions increased significantly.[142] Wascher et al conducted a more specific study to determine the effect of a low-dose of L-arginine administered intravenously on insulin sensitivity in healthy, obese, and type 2 diabetic subjects. L-arginine (0.52 mg/kg/min) restored the impaired insulin-mediated vasodilation observed in patients with obesity and type 2 diabetes and improved insulin sensitivity in all three groups studied.[143]

Other Supplements

Glutathione

Individuals with type 2 diabetes appear to have abnormal intracellular reduced glutathione (GSH) redox status.[144] Evidence also suggests whole-body glucose disposal is associated with intracellular GSH redox status.[138] In order to assess the impact of GSH on insulin sensitivity, De Matta et al administered glutathione ($1.35 \text{ g x m}^2/\text{min}$) intravenously to 10 subjects with type 2 diabetes and 10 healthy subjects for one hour and repeated this protocol one week later. Both groups experienced increased glucose uptake, suggesting enhanced insulin sensitivity, and an improved intracellular GSH redox status.[144]

Fish oils

While fish oils, rich in omega-3 essential fatty acids (omega 3 EFAs), improve insulin resistance in animal models,[145] their effect in humans has been equivocal. Available human research has shown a range of outcomes regarding insulin metabolism ranging from some improvement to no change to deterioration of glycemic control in one study.

Bhathena et al fed 40 healthy men diets providing 40 percent of calories from fat. During the fish oil intervention period, the men received 15 gm/day fish oil concentrate for the

full 10 weeks of the trial and 200 mg vitamin E for the last eight weeks. Compared with the placebo period (15 gm/day mixed fat and 25 mg/day vitamin E), the intervention resulted in decreased insulin,[146] suggesting the possibility that insulin resistance had improved.

In two trials of fish oil supplementation in people with type 2 diabetes, similar results were not obtained. Borkman et al investigated the effects of fish oil administration in individuals with mild type 2 diabetes. They fed 10 subjects a standard diabetic diet throughout their trial and, using a double-blind crossover design, provided either 10 gm fish oil concentrate (30-percent omega 3 EFAs) daily, or 10 gm safflower oil daily over separate three-week periods. They found no change in either fasting serum insulin levels or insulin sensitivity. They also observed a 14-percent increase in fasting blood glucose following the fish oil intervention, suggesting a possible adverse effect on glycemic control, at least in this patient population.[147]

Rivellese et al also conducted a randomized double-blind, placebo-controlled trial of fish oil as an intervention for individuals with type 2 diabetes. The treatment group received 2.7 g/day eicosapentaenoic plus docosahexaenoic acid for two months, followed by 1.7 g/day for four additional months. During the trial, diet and hypoglycemic drugs remained unchanged. Although supplementation resulted in an improvement in some parameters associated with cardiovascular risk, no significant difference in blood glucose control or insulin sensitivity was observed between the fish oil and placebo groups. While the investigators found no deterioration of blood glucose control, this dose of fish oils was unable to modify insulin resistance in this patient population.[148]

Coenzyme Q10

Coenzyme Q10 (CoQ10) is a promising nutritional intervention for insulin resistance, at least among subjects with hypertension. Singh et al conducted an eight-week randomized, double-blind trial comparing the use of a water soluble form of CoQ10 (60 mg twice daily) to a vitamin B complex in 59 hypertensive patients. Their results indicated CoQ10 at this dose lowered glucose and fasting insulin levels, suggesting possible improved insulin resistance. CoQ10 supplementation also resulted in improvements in blood pressure, lipid profiles, and blood levels of the antioxidant vitamins A, C, E, and beta carotene. Measured parameters associated with oxidative stress decreased with CoQ10 supplementation. The only observed changes in the group taking the B-vitamin complex were increases in vitamin C and beta carotene.[149]

α-Lipoic Acid

a-Lipoic acid has been shown to improve insulin resistance in a variety of animal models.[150,151] Experimental trials have also provided evidence that lipoic acid might be useful in the treatment of insulin resistance in humans under some circumstances.

Clinical studies have described an increase of insulin sensitivity after both single infusion and short-term parenteral administration of lipoic acid. At a single parenteral dose of 1000 mg, Jacobs et al reported lipoic acid resulted in a significant increase in insulin-stimulated glucose disposal among subjects with type 2 diabetes, increasing the metabolic clearance rate for glucose by about 50 percent.[152] Jacobs et al, in a subsequent uncontrolled trial, administered a daily infusion of lipoic acid (500 mg/500 ml NaCl, 0.9%) to 20 subjects with type 2 diabetes for 10 days. Following the treatment period, an approximately 30-percent increase in insulin-stimulated glucose disposal was observed.[153]

Results also suggest oral administration of a-lipoic acid can improve insulin sensitivity in patients with diabetes. Jacob et al

Table 4: Hypertension and Insulin Resistance: Interventions

Intervention	Dose	Comments
Fiber	Increase	In general, higher fiber diets associated with improved insulin resistance.
Saturated Fat	Decrease	In general, high saturated fat diets associated with worsening of insulin resistance.
Vegetables	Increase	In general, evidence suggests high blood levels of carotenoids inversely associated with fasting insulin
Vitamin A-rich foods	Increase	Diets higher in vitamin A have shown an inverse relationship with insulin resistance.
Salt Intake	Low-Moderate	Salt avoidance and high salt intake might worsen insulin resistance.
Nicotine Containing Products	Decrease	Use of nicotine-containing products associated with worsening of insulin resistance.
Exercise	Increase	Exercise is critical for preventing and reversing insulin resistance.
Stress	Decrease	Acute stress associated with insulin resistance. Chronic psychosocial stress probable association with insulin resistance.
Magnesium	Not Studied	Higher magnesium level corresponds to a greater degree of sensitivity to insulin.
Calcium	1500 mg/d	Improved insulin sensitivity.
Potassium	Not Studied	Diet inducing potassium depletion results in a resistance to insulin action.
Vitamin E	600 mg/d	Improved insulin sensitivity.
CoQ10	60 mg bid	Improvements suggestive of increased insulin sensitivity.

investigated the effect of a four-week placebo-controlled, multicenter pilot study to determine the effectiveness of oral treatment with lipoic acid on insulin sensitivity in people with type 2 diabetes. Seventy-four patients were randomized to either placebo or active treatment consisting of lipoic acid in doses of either 600 mg once daily, twice daily, or three times daily. Prior to treatment, all four groups had comparable degrees of hyperglycemia and insulin sensitivity. While not all treated subjects experienced improvements, a mean increase of 27 percent in insulin-stimulated glucose disposal was observed among subjects receiving supplemental lipoic acid. However, no statistical differences in insulin sensitivity appeared among subjects receiving the higher doses of lipoic acid, suggesting the lack of a dose-dependent response above 600 mg, and that an optimal dose is 600 mg daily or lower.[154]

In another study, Konrad et al evaluated the effect of a-lipoic acid on insulin sensitivity and glucose metabolism in lean and obese individuals with type 2 diabetes. Subjects were given an oral dose of 600 mg lipoic acid twice daily for four weeks. Both groups had improvements in measured aspects of glucose metabolism suggestive of an enhanced effectiveness of supplementation on insulin sensitivity.[155]

Table 5: Obesity and Insulin Resistance: Interventions

Intervention	Dose	Comments
Fiber	Increase	In general, higher fiber diets associated with improved insulin resistance.
Guar Gum	NA	Unable to alter insulin sensitivity at either 4 or 8 grams bid.
Saturated Fat	Decrease	In general, high saturated fat diets associated with worsening of insulin resistance.
Monounsaturated Fats	Increase	Not studied in obese subjects but among type 2 diabetic subjects it promotes weight loss and improvement in waist/hip ratio.
Vegetables	Increase	In general, evidence suggests high blood levels of carotenoids inversely associated with fasting insulin.
Vitamin A-rich foods	Increase	Diets higher in vitamin A have shown an inverse relationship with insulin resistance.
Salt Intake	Moderate	Extremes of salt intake (low or high) appear to worsen insulin resistance.
Nicotine-Containing Products	Decrease	Use of nicotine-containing products associated with worsening of insulin resistance.
Exercise	Increase	Exercise is critical for preventing and reversing insulin resistance.
Stress	Decrease	Acute stress associated with insulin resistance. Chronic psychosocial stress probable association with insulin resistance.
Magnesium	Not Studied	Deficiency likely.
Potassium	Not Studied	Diet inducing potassium depletion results in a resistance to insulin action.
Zinc	Not Studied	Association between low zinc levels and insulin resistance.
Chromium Picolinate	NA	Resistance training-enhanced insulin sensitivity; however, chromium picolinate (924 mcg/d) showed no ability to add to these positive effects.
L-arginine	Unknown	I.V. administration improves insulin sensitivity, but oral dosage and chronic administration unstudied.
Lipoic acid	600 mg/d	Improved insulin sensitivity in obese type 2 diabetic subjects.

Botanicals

An antioxidant flavonoid component of *Silybum marianum* (Milk Thistle), silymarin appears to offer potential for improving insulin resistance, at least under some clinical circumstances. Velussi et al conducted a study to determine whether long-term treatment with silymarin was effective in reducing lipid peroxidation and insulin resistance in diabetic patients with alcoholic cirrhosis. In addition to standard treatment, 30 subjects were given 600 mg silymarin daily, while a matched control group received standard therapy alone. Treated subjects exhibited a significant decrease in fasting blood glucose, mean daily blood glucose, daily glucosuria, and fasting insulin levels noticeable after four months of therapy. Subjects in the silymarin group were

Table 6: Type 2 Diabetes and Insulin Resistance: Interventions

Intervention	Dose	Comments
Fiber	Increase	In general, higher fiber diets associated with improved insulin resistance
Guar Gum	4 g bid	Improves insulin sensitivity. Decreases fasting insulin levels.
Saturated fat	Decrease	In general, high saturated fat diets associated with worsening of insulin resistance.
Monounsaturated Fats	Increase	Improves insulin sensitivity.
Vegetables	Increase	In general, evidence suggests high blood levels of carotenoids inversely associated with fasting insulin.
Vitamin A-rich Foods	Increase	Diets higher in vitamin A have shown an inverse relationship with insulin resistance.
Salt Intake	Moderate	Extremes of salt intake (low or high) appear to worsen insulin resistance.
Nicotine-Containing Products	Decrease	Use of nicotine-containing products associated with worsening of insulin resistance.
Exercise	Increase	Exercise is critical for preventing and reversing insulin resistance.
Stress	Decrease	Acute stress associated with insulin resistance. Chronic psychosocial stress probable association with insulin resistance.
Magnesium	To correct deficiency	Deficiency likely, but replenishment unlikely to improve insulin resistance.
Potassium	Not Studied	Diet inducing potassium depletion results in a resistance to insulin action.
Zinc	Not Studied	Association between low zinc levels and insulin resistance.
Chromium Picolinate	200-500 mcg bid	Mixed results reported.
Vanadyl Sulfate	100 mg/d	Improves insulin sensitivity.
Vitamin E	NA	Vitamin E (600 mg/d) resulted in a decrease in the glucose disposal rate suggesting a worsening of insulin resistance.
L-carnitine	Unknown	I.V. infusion improves insulin sensitivity, but oral dosage and chronic administration unstudied.
L-arginine	Unknown	I.V. administration improves insulin sensitivity, but oral dosage and chronic administration unstudied.
Glutathione	Unknown	I.V. administration improves insulin sensitivity, but oral dosage and chronic administration unstudied.
Lipoic acid	600 mg/d	Improves insulin sensitivity.

also able to lower their exogenous insulin requirements. During the same period of time, the control group had worsening fasting insulin levels and a stabilized insulin need.[156]

It is likely other herbal medicines might have therapeutic potential for modifying insulin resistance. As an example, research indicated that *Inula racemosa* improved glucose metabolism in experimental animals, and that this activity was probably secondary to potentiation of insulin sensitivity in peripheral tissues.[157] More research is required to determine if any of the plant medicines currently used in diabetes management will play an eventual therapeutic role in insulin resistance.

Conclusion

A great deal more research is required to determine an ideal approach to both prevention and reversal of insulin resistance. Since lifestyle factors play such a prominent role in insulin resistance, modifying potential contributing habits should be a priority in the management of insulin resistance. Minerals such as magnesium, calcium, potassium, zinc, chromium, and vanadium appear to have association with insulin resistance or its management. Amino acids, including L-carnitine, taurine, and L-arginine, might also play a role in the reversal of insulin resistance.

Table 7: Healthy (non-obese and non-diabetic) Subjects with Insulin Resistance: Interventions

Intervention	Dose	Comments
Fiber	Increase	In general, higher fiber diets associated with decreased insulin resistance
Guar Gum	10 g tid	Improves insulin sensitivity.
Saturated Fat	Decrease	In general, high saturated fat diets associated with insulin resistance.
Vegetables	Increase	In general, evidence suggests high blood levels of carotenoids inversely associated with fasting insulin.
Vitamin A-rich Foods	Increase	Diets higher in vitamin A have shown an inverse relationship with insulin resistance.
Salt Intake	Moderate	Extremes of salt intake (low or high) appear to worsen insulin resistance.
Nicotine-Containing Products	Decrease	Use of nicotine-containing products associated with worsening of insulin resistance.
Exercise	Increase	Exercise is critical for preventing and reversing insulin resistance.
Stress	Decrease	Acute stress associated with insulin resistance. Chronic psychosocial stress probable association with insulin resistance.
Magnesium	4.5 g per day	Improved insulin sensitivity. Note: this very high dose would likely act as a cathartic.
Potassium	Not Studied	Diet inducing potassium depletion results in a resistance to insulin action.
Zinc	Not Studied	Association between low zinc levels and insulin resistance.
Chromium Picolinate	200 mcg	Observed changes suggestive of improved insulin sensitivity.
L-carnitine	Unknown	I.V. infusion improves insulin sensitivity, but oral dosage and chronic administration unstudied.
L-arginine	Unknown	I.V. administration improves insulin sensitivity, but oral dosage and chronic administration unstudied.
Glutathione	Unknown	I.V. administration improves insulin sensitivity.

Other nutrients, including glutathione, coenzyme Q10, and lipoic acid, also appear to have therapeutic potential. Research on herbal medicines for the treatment of insulin resistance is limited; however, silymarin has produced positive results in diabetic patients with alcoholic cirrhosis, and *Inula racemosa* potentiated insulin sensitivity in an animal model.

Based on available research, ideal protocols for reversing insulin resistance should take into account existing complicating factors such as type 2 diabetes, hypertension, obesity, cirrhosis, or dialysis. In other words, the ideal regimen for reversing insulin resistance might likely vary for an individual with type 2 diabetes and a non-diabetic obese individual. For a summary of protocols for various subgroups of people with insulin resistance see Tables 4-7.

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