Insulin Resistance, Glucose Intolerance and Metabolic Syndrome

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A Health Crises

In America, and the rest of the world is not far behind, we are facing a health crisis of unparalleled scope. "Metabolic Syndrome" and all of its co-morbidities have spiraled out of control and continue to get worse, not better every year. We cannot afford to keep doing the same things with the same mindset and expect a different outcome (definition of 'insanity'?). In other words we must not be content to merely treat the symptoms while ignoring the underlying pathophysiology of the cause.

BACKGROUND

This paper reviews the findings of clinical studies and the direct experience WiO has recorded with thousands of patients. The findings of these studies have already identified promising relief from the exploding epidemic of Metabolic Syndrome that is washing over America and the rest of the world. The WiO Diet is a medically designed protocol that is the result of nearly 4 years of studying and researching over 600 clinical studies spanning 50+ years and additional beta testing in 6 clinics with over 1,000 patients within an 18-month time period.

After intensive study of over 600 clinical studies, we created a database of relative findings from the studies listing the correlating conclusions that were in harmony with each other. The areas of focus were: 1-metabolic interaction in relationship with the symptoms of metabolic syndrome, 2- primary organs involved, 3- effects of macro & micro-nutrients, and 4-psychological impact & treatment for a term lifestyle change.

We then set up 6 separate beta test clinics in existing businesses specializing in: general medicine, chiropractic, nutritional products, physical/exercise training, health spa, and health counseling. We have designed a 4-phase protocol covering 18 weeks. Phase 1 is 4 meals per day, three of which are controlled by a meal-replacement formula (MRP) provided by WiO. In Phase 2 and 3 the MRP meals are reduced to 2 then 1 per day, respectively. Phase 4 is a maintenance phase with one MRP meal daily. WiO provides nutritional education and resources on how to emotionally establish a healthy relationship to food, called "Intuitive Eating."

As can be expected with any weight loss, certain physiological parameters will improve. Blood pressure, total cholesterol, and fasting glucose will be reduced. In the beginning of our research, we expected these physiological improvements, but you could expect these improvements from any successful weight loss program. Within a few weeks and months, we noticed other patterns that were pleasing but couldn't be explained by weight loss alone. Dieters reported a greater amount of energy, were actually stronger, and experienced better digestion (including GERD), relief from inflammation issues, significant mood enhancement, and even some cases of sleep apnea were resolved or improved.

Dieters were reporting that they had better ability to concentrate, and their skin and nails were better. We were amazed by one account of a 63-year-old man that had suffered from type II diabetes for 12 years. His average daily glucose readings had dropped from 347 to 75 (-78.4%) in the first 7 days. This dieter did not have a weight issue which indicated that his blood sugar was affected by something other than weight loss. Equally satisfying, but puzzling was that this was occurring just one week into the program. Many of our high blood pressure dieters were reporting extreme dizziness in the first 7-10 days: their high blood pressures had dropped so fast, that their prescription had to be reduced. Weight loss alone could not explain these results – not with only losing a small percentage of their total body weight in a matter of days.

What is Insulin?

Insulin is a hormone that your pancreas creates. This hormone helps maintain proper blood sugar levels. Insulin helps the cells absorb glucose, reducing blood sugar and providing the cells with glucose for energy. When blood sugar levels are too low, the pancreas releases glucagon.

What is Glucose?

Glucose comes from the Greek word for "sweet." It's a type of sugar you get from foods you eat, and your body uses it for energy. As it travels through your bloodstream to your cells, it's called blood glucose or blood sugar. Insulin is a hormone that moves glucose from your blood into the cells for energy and storage.

What is Glucagon?

Glucagon is a hormone that is involved in controlling blood sugar (glucose) levels. Glucagon instructs the liver to release stored glucose, which causes blood sugar to rise.

What is Insulin Resistance?

It is estimated that at least 50% of Americans have insulin resistance. Insulin resistance is what happens when your body doesn't respond correctly to insulin. This incorrect response causes your body to need the pancreas to produce more insulin.

As your pancreas makes more insulin, your body continues to resist and respond incorrectly to the higher levels of insulin. Your pancreas will continually need to make more to compensate. Eventually, your

pancreas won't be able to keep up with the amount of insulin your body needs to keep your blood sugar at a healthy level. Insulin resistance can eventually lead to type 2 diabetes.

What is Glucose Intolerance?

It has been determined that as much as 44.1% of Americans have a level of intolerance to glucose. Generally, this means that when carbs are consumed their cells and pancreas respond in a hyperbolic manner. Because these individuals blood glucose levels overreact when carbs are eaten, in like manner, these people will also react with higher levels of insulin, which worsens the symptoms of metabolic syndrome. Glucose intolerance is a term for metabolic conditions which result in high blood glucose levels. Pre-diabetes, type 2 diabetes, impaired fasting glucose and impaired glucose tolerance are all conditions which fall under the term glucose intolerant.

Food - Insulin and Glucagon

Table 1[48] shows the effects of different combinations of macronutrients on our body's production of insulin and glucagon. The goal is to strive for a balance between glucagon and insulin, a diet with a little more protein and fat (EFA balance) with fewer carbohydrates would seem to be required. After review, it is clear that the food combinations are more interesting. A meal of high carbohydrates and fat, with little protein, will likely produce a veritable flood of insulin and very little, if any, glucagon. Consider your menus at home, those in restaurants and in the schools we send our children to. Our children's favorite foods; soda, even juice, macaroni and cheese, pizza, peanut butter and jelly, cheese and crackers, just to name a few of their favorites. All of these are high in carbohydrates and fat and have very little, if any, protein, thus, they promote a dominance of insulin rather than a balance of both hormones.

Influence of Food on Insulin and Glucagon

Type of food	*Insulin*	*Glucagon*
Carbohydrate	+++++	no change
Protein	++	++
Fat	no change	no change
Carbohydrate and Fat	++++	no change
Protein and Fat	++	++
High Protein and Low Carb	++	+
High Carb and Low Protein	++++++++++	+

TABLE 1

The Roles of Insulin and Glucagon

TABLE 2: INSULIN - GLUCAGON

Table 2[48] lists the effects insulin and glucagon have on our physiological processes. It is pretty obvious that "spending more time" under glucagon's influence would be preferable, yet the vast majority of North Americans diet ensures the opposite. There are individuals that eat like this and apparently don't suffer with the clutches of Metabolic Syndrome. However, evidence is showing that for a growing number of individuals (the majority), these effects are all too painfully apparent.

The Roles of Insulin and Glucagon

Insulin	*Glucagon*
Lowers elevated blood sugar	***Raises*** low blood sugar
Shifts metabolism into ***storage*** mode	Shifts metabolism into ***burning*** mode
Converts glucose and protein to fat	Converts protein and fat to glucose
Converts dietary fat to ***storage***	Converts dietary fat to ketones and sends them to the tissues for ***energy***
Removes fat from blood and transports it into fat cells	Releases fat from fat cells into blood for use by tissues as energy
Increases the body's production of ***cholesterol***	***Decreases*** the body's production of ***cholesterol***
Makes the kidneys ***retain*** excess fluid	Makes the kidneys ***release*** excess fluid
Stimulates ***growth*** of arterial smooth muscle cells	Stimulates ***regression*** of arterial smooth muscle cells
Stimulates the use of ***glucose for energy***	Stimulates the use of ***fat for energy***

TABLE 2

THE RELATIONSHIP BETWEEN INSULIN AND GLUCAGON IN THE PATHOGENESIS OF "METABOLIC SYNDROME"

By Michael P. Ciell, R.Ph.

WHAT IS "METABOLIC SYNDROME"

A commonly accepted definition "Metabolic Syndrome" might be a generalized disorder whose four hallmark symptoms are hyperglycemia, hyperlipidemia, hypertension and obesity. Presenting with two of the above is generally considered the diagnostic criteria for this disorder. Gerald Reaven, MD (Professor Emeritus - Active of Medicine at Stanford University) was the first to use the term in 1988, saying he preferred it to names like "Metabolic Syndrome" or the "Deadly Quartet". He said, "Many of the manifestations of the disorder might not be considered 'metabolic' (i.e. increases in plasminogen activator inhibitor –1 (PAI-1) a factor regulating the process of fibrinolysis), and the 'Deadly Quartet' implies obesity is an essential component while many very obese persons may have nothing resembling the syndrome (Sumo wrestlers may be an example)."

Semantics aside, the real significance of Dr. Reaven's work was to establish, for the first time, the link between insulin resistance (primarily with regard to insulin stimulated glucose disposal by muscle and insulin regulation of lipolysis in adipose tissue) and the four hallmark symptoms of this syndrome. He reasoned that insulin's first function

will always be to mediate glucose uptake by the muscles. If glucose levels remain elevated (due to the muscles' insulin resistance) the pancreas will continue to produce more insulin in an attempt to control the high glycemia. Complications now appear because many of the other tissues/organs still retain their sensitivity to insulin. The kidney is a good example. Insulin stimulates sodium retention by the kidney, thus contributing to water retention and hypertension. Dr. Reaven cites polycystic ovary syndrome (hypersecretion of androgens from the ovary) as another example of insulin sensitive organs being affected [1]. Basically the ovary, being constantly exposed to higher than normal levels of insulin, increases its testosterone production accordingly. Thus, the insulin resistance of one tissue with the compensatory hyperinsulinemia that ensues will lead to many other insulin sensitive tissues being affected and complicating the entire physiological picture of that individual. Our complete understanding of this principle is necessary so that a protocol addressing the cause of the problem may be designed, instead of merely treating the symptoms as isolated and unrelated pathologies. According to Dr. Reaven, "The manifestations of Metabolic Syndrome" can be divided into six major categories:

1. Glucose intolerance: Individuals with Metabolic Syndrome don't have diabetes, by definition, but their plasma glucose concentration is higher than those individuals who don't have Metabolic Syndrome.

2. Dyslipidemia: The characteristic findings are high plasma triglycerides and low HDL-cholesterol. The insulin resistance and compensatory hyperinsulinemia cause the liver to produce more triglyceride rich VLDL, thus increasing the plasma triglyceride concentration. Cholesterol ester transfer protein (CETP) transfers cholesterol from HDL to VLDL, exchanging it for triglycerides. Therefore, the HDL cholesterol falls. The increased VLDL also reduces the ability to remove postprandial newly absorbed chylomicrons. In Metabolic Syndrome, VLD, chylomicrons and their metabolic remnants (chylomicron and VLDL remnants) are removed more slowly from the plasma by virtue of their increased concentrations, resulting in increased postprandial lipemia. In addition, there is a shift in the LDL particle diameter to smaller and denser LDL particles.

3. Uric acid metabolism: There is a tendency to increased serum uric acid concentration. There is a decrease in the ability of the kidney to excrete uric acid; therefore, renal uric acid clearance is decreased.

4. Kidney manifestation: There is an increased salt retention. It appears that half the patients with hypertension are insulin resistant. From population-based studies, the best predictor of hypertension developing has been hyperinsulinemia as a surrogate measure of insulin resistance.

5. Hemodynamic manifestations: There is evidence that the sympathetic nervous system activity is increased in insulin resistant individuals. This is another example of other tissues reacting to the hyperinsulinemia.

6. Fibrinolytic changes: There is an increase in PAI-1, with a resultant decrease in fibrinolysis. The increase in fibrinogen tends to increase coagulation. All of these manifestations can have some role in the development of coronary heart disease.[2] As Dr. Reaven points out; the insulin resistant/hyperinsulinemic patient is at a greatly increased risk for developing CHD. Let's briefly look at insulin's role in the mechanisms involved in the etiology of hypertension and CHD. Michael P. Ciell, R.Ph.

Keeping Carbohydrates Low Changes the Biochemical Pathway

Now, let's observe how the metabolic pathways are altered simply by changing the ratio of macronutrients (Fat – Protein – Carbohydrates) in the diet. Again referring to Table 1 (page 4), we will see that if we keep the carbohydrates low and increase the amount of fat and protein; we will have a huge effect on the ratio of insulin to glucagon. Following a meal, the blood glucose rises and insulin is secreted. The glucose begins to enter the muscle cells; however due to the consumption of few carbohydrates, the ready supply of glucose in the blood soon begins to decrease. This is particularly profound in IR /hyperinsulinemic individuals and the phenomenon is called "reactive hypoglycemia". When the blood glucose falls to a certain level, the pancreas will instead secrete glucagon and the adrenals secrete epinephrine (also known as adrenaline), norepinephrine and cortisol (stress hormones – each serving of MRP has Ashwagandha which has clinically been shown to reduce cortisol by 31%) as it attempts to maintain homeostasis with respect to blood glucose levels. The first effect of glucagon is to immediately stop the secretion of insulin. The next effect is to cause the liver and skeletal muscles (glycogen storage 80-90% liver 10-20% muscle) to release some glycogen, which will be converted into glucose. More importantly, the triglycerides now become a source of energy.

Keeping the insulin levels low by dietary means will improve insulin sensitivity in hyperinsulinemic/IR patients. You absolutely have the ability, not only to improve the symptoms of "Metabolic Syndrome" but also the method to begin to reverse it. Year after year, study after study, and our own clinical experience plus that of hundreds of other practitioners has done nothing but confirm the above-mentioned physiological improvements. A paper published in the New England Journal of Medicine in May 2003 concluded this: "Severely obese subjects with a high prevalence of diabetes or the Metabolic Syndrome lost more weight during 6 months on a carbohydrate-restricted diet than on a calorie and fat-restricted diet, with a relative improvement in insulin sensitivity and triglyceride levels, even after adjustment for the amount of weight lost." [35]

Conclusions from a study published in the Annals of Internal Medicine in May 2004 echoed the same opinion: "Compared with a low-fat diet, a low-carbohydrate diet program had better participant retention and greater weight loss. During active weight loss, serum triglyceride

levels decreased more, and high-density lipoprotein cholesterol levels increased more with a low-carbohydrate diet than with a low-fat diet." [36] Gerald M. Reaven, MD (the one who first coined the term "Metabolic Syndrome" more commonly known as Metabolic Syndrome) summed up nicely his experience with hyperinsulinemic/IR patients on a high carbohydrate/low fat diet versus a low carbohydrate/high fat diet in a 2001 article published in San Francisco Medicine.[37]

Dr. Reaven states that "the most dramatic improvements in the manifestations of Metabolic Syndrome occur in overweight, insulin resistant/hyperinsulinemic individuals when they lose weight. However, there appears to be little or no evidence, as long as the energy content is kept constant, that low fat/high carbohydrate diets will directly improve insulin sensitivity. On the other hand, **there is considerable evidence that isocaloric diets low in fat and enriched in carbohydrates will accentuate the manifestations of Metabolic Syndrome.** The more insulin resistant an individual, the greater is the amount of insulin that must be secreted in response to a carbohydrate-enriched diet in order to maintain glucose homeostasis.

Thus, the inevitable and consistently replicated effect of replacing saturated fat with carbohydrates in insulin resistant individuals is to increase the concentration of triglyceride-rich lipoproteins, both fasting and postprandial. The increase in the ambient TG-rich lipoproteins seen following low fat/high carbohydrate diets is associated with a decrease in HDL-cholesterol concentration; and more recently, it appears that such diets will convert the LDL to VLDL in half the individuals who had either high LDL or an intermediate pattern at the outset. Given the evidence that low fat/ high carbohydrate diets do not modify the basic defects in Metabolic Syndrome (insulin resistance) and accentuates all of its metabolic manifestations, there seems to be little rationale for substituting saturated fat with carbohydrates. This is particularly true in light of the multiple observations that replacing saturated fat with mono-saturated or polyunsaturated fat, or both, will lead to the same decrease in LDL cholesterol without any of the adverse metabolic effects seen with low fat carbohydrate diets." [38, 39]

Insulin and Glucagon: Regulators of the Eicosanoid Pathways

One of the most important things a person can do to influence the types of eicosanoids produced is to balance his or her levels of insulin and glucagon. These two master hormones have a profound effect on eicosanoid synthesis and once again we will see the benefit of living life "on the glucagon-dominant side of the street". The WIO Protocol has yielded wonderful benefits not only with regard to weight control and diabetes, but also with those who suffer from such diseases as hypertension, asthma, COPD, acid reflux and immune disorders to name a few. Of course for the IR/hyperinsulinemic individual, the program can be a God-send.

Let's return to the discussion of 'the flow of fat' with the free fatty acid inside the cytoplasm of the cell (other than a fat cell). Let's remember that FFA can be directed into the mitochondria where it is oxidized for energy or will be incorporated into the cellular membrane. These functions happen under glucagon's influence. If insulin is dominant, the FFA may be directed to the adipocyte for storage or may be used in the de novo synthesis of cholesterol should the cell require that; but if this FFA happens to be a molecule of ***linoleic acid*** (LA), the most common omega-6 oil in the American diet, it may be used in the synthesis of eicosanoids. This process begins with the body activating the enzyme ***delta 6 desaturase*** (D6D) which is the initiating step of eicosanoid production and, by the way, requires a lot of energy. Factors such as disease, aging, stress and a diet high in ***trans-fats*** (basically metabolic poisons) or a diet high in carbohydrates will hinder this first step. Conversely, a diet containing an adequate supply of a quality protein will enhance the activity of this important first step and ensure a good flow of LA into the eicosanoid production line.[41] The WIO Protocol does a marvelous job in this respect: very low in carbohydrates, no trans-fats and high quality, non-GMO easily absorbable protein. The molecule of linoleic acid (LA) now begins its biochemical transformation into an eicosanoid. There are a few preliminary steps (called ***elongation***) which involve the attachment of additional carbon atoms to the original LA molecule to bring the total number of carbon atoms to twenty.

At this stage, another enzyme, delta 5 desaturase or D5D, may act on our 'blossom-ecosanoid'. If D5D does in fact react with this fatty acid, it will soon be transformed to ***arachidonic aAcid*** (AA), and will be on the way to becoming one of the "undesirable series two eicosanoids". **Insulin, very strongly, forces this metabolic pathway.**

However, if glucagon is present, this enzyme is suppressed, and the fatty acid will be directed to become a series one eicosanoid. Remember, we do not want to inhibit either of these biochemical pathways (Bextra® and Vioxx® are great examples of this-an idea that 'looked good on paper but had disastrous clinical results), but **we do want to influence which is the predominant pathway**. In your practice, you will encounter patients who are, of course elderly, suffering from a chronic condition or who are excessively 'insulin-dominant'. These factors will no doubt impede the entry of LA into the 'eicosanoid production line' and the full benefits of the "WIO Protocol" will not be realized. There is a solution for such problems.

If we add an omega-3 oil supplement to their diet, we can affect a neat biochemical "trick". The enzyme D5D preferentially binds to the omega-3 oils rather than the omega-6 oils (like LA). So, in these cases, where insulin is predominant and is directing this enzyme to attach to LA, some of the enzyme available binds to the omega-3 oils and less arachidonic acid (the precursor to the series two eicosanoids will be produced and more of the series one eicosanoids 'the good guys') will be made. Incidentally when D5D attaches to an omega-3 oil, a subclass of eicosanoids (the series three eicosanoids) is formed. These are nei-

ther pro or anti-inflammatory but rather modulate the degree to which the series one or series two eicosanoids express themselves. These are also very beneficial in terms of clinical outcomes.

Occasionally there are some who, despite very good success with the WIO Protocol (good weight loss, improved blood lipids and glucose levels), may not appear to be doing as well in other respects. For instance, their blood pressure, although improved due to the weight loss and reduction in insulin levels, may not as be as good as others on the same protocol. This small sub-class of people may be extra sensitive to arachidonic acid. The Eades[42] advise you to watch for these main symptoms often associated with high levels of arachidonic acid or show sensitivity to it:

- Chronic fatigue
- Poor or restless sleep
- Difficulty awakening or grogginess upon awakening
- Constipation
- Brittle hair and/or thin, brittle nails
- Dry, flaking skin
- Minor rashes

Eliminating dietary sources of AA may prove very beneficial to these individuals. AA is found in all meats, particularly red meats and organ meats. It is also found in egg yolks. Having these patients use only egg whites (or only one whole egg and remainder of the dish of just egg whites) will help reduce AA levels. Substituting wild game (if available) instead of grain-fed, commercially raised livestock and instructing them to trim off the fat will also help decrease dietary sources of AA. The fat of grain–fed beef will always contain more AA than free-range, grass-grazed animals, as the diet of grain will raise insulin levels in these animals contributing to a greater synthesis of AA in vivo. Using coconut oil or clarified butter in sautéing as opposed to seed or vegetable oils will also prove beneficial.

Keeping Hormones Simple

As a basic refresher: a hormone is any chemical that can transmit information - essentially hormones are messengers. Within our body lies a biological "internet" that is vastly more complex and numerous than the Internet and it's millions of users. To put it in perspective you would have to have over 30,000 planet Earths all on the internet to equal the sum of sixty trillion cells needed to maintain constant communication with one another. Our body's communication system is controlled by hormones, which are and can be modified by the WiO Diet Program.

How We Control Your Hormones

Ultimately we are showing your body how to repair, balance and control this ultra-complex bio-chemical network with a very simple solution: by consuming 3 MRP's shakes per day in Phase 1 of the WiO Protocol. Here's what we have learned in our clinics and from clinical studies about controlling our hormones:

1. Balance protein and carbohydrates at every meal - this will control insulin levels .
2. Calorie restriction without hunger or deprivation - this is a proven way to increase longevity.
3. Supplementation with WiO Pro Omega Oil - this alters eicosanoid production.

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