Functional Medicine Approach to Identification and Management of Insulin Resistance: A Literature Review

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Abstract

Objective: To determine the most efficient and productive way to evaluate and treat insulin resistance and therefore preventing many of its symptomatic effects.

Data Collection: Peer reviewed journals, research articles, and book publications were compiled and a computer search of PubMed, Google Scholar, EBSCO Host, and the Logan College of Chiropractic Library for articles containing relevant information on functional laboratory evaluation and treatment of insulin resistance. Information was sought concerning herbs, minerals, the effects of certain heavy metal toxicity, vitamins and their role in insulin resistance.

Conclusion: There are several ways of determining if an individual is having difficulty with sugar regulation and this review uncovered serveral interventions to increase ones glucose tolerance. Eating a balanced low glycemic diet and supplementing with herbs and minerals that are synergistic to insulin is the best way to prevent Insulin Resistance.

Key Words: Functional Medicine, Diet, Insulin Resistance, Metabolic Syndrome, Syndrome X, Copper Toxicity, Mineral Imbalance, Gluten intolerance, Glucose dysregulation

Introduction

Insulin resistance, also known as metabolic syndrome and syndrome X, is a problem with the body's ability to react to insulin. The body reacts to this by producing more insulin. This increase in insulin can create many different problems in the body, such as, hypoglycemia, weight gain (especially around the waist), hirsutism in women (excessive facial hair or developing male hair pattern traits), skin tags, acne, acanthosis nigracans (velvety, light-brown-to-black, markings usually on the neck, under the arms or in the groin), alopecia areata (scalp and/or body hair loss), depression and mood swings, yeast infections, sleep disturbances, lethargy, changes in menstrual cycles, bloating, high LDL (bad cholesterol) and low HDL (good cholesterol), high levels of triglycerides, high blood pressure, food cravings - especially for carbohydrates. According to a study at Hitachi Health Care Center, Ibaraki, Japan, participants in a health screening program who underwent abdominal CT measurement, were found to have increased odds of early colorectal cancer in subjects with greater visceral fat mass, but not in those with greater subcutaneous fat mass. Markers of insulin resistance were also associated with a higher prevalence of colorectal cancer.22 Excessive insulin in the body, or hyperinsulinemia, is also a precursor for Type 2 diabetes and heart disease. Therefore, the earliest identification and the treatment of this syndrome would be beneficial to the patient and could prevent some of the major diseases that we face in the United States. The chiropractic approach to patient care is to focus on the neurological deficits caused by spinal misalignments. Chiropractic patients often present with underlying insulin resistance and this could be causing or exacerbating their presenting complaint. Functional Medicine (FM) is an excellent way to evaluate this condition, by looking beyond the signs and symptoms. FM takes a functional approach by employing laboratory assessments and looking at environmental inputs, such as diet and nutrients (including water), exercise, trauma, and biochemical individuality.

The literature describes the occurrence of insulin resistance and its related disorders. It demonstrates how some other conditions can be directly related to insulin resistance and how these conditions can be avoided or controlled by diminishing the insulin resistance. Disorders such as polycystic ovarian syndrome and diseases such as Type 2 Diabetes (which is the most common non-communicable disease in the world), and Coronary Heart Disease are intimately linked to insulin insensitivity. Using a mathematical simulation model, some researchers estimated that insulin resistance was responsible for 42% of myocardial infarctions in the U.S. and was the most important single cause of coronary artery disease. 23 Cognitive decline is a risk of insulin resistance because of the adverse impact of inflammatory mediators on neuronal function. Many things can contribute to insulin resistance and have to be considered, such as, diet, obesity, inactive lifestyle, overconsumption of caffeine, mineral imbalances, certain medications, heavy metal toxicity, pregnancy, and other hormonal imbalances. Chiropractic typically follows a wellness based approach to healthcare as they interest their patients in diet, supplementation, exercise, adequate rest, and other wide ranging topics to promote overall wellness. Functional Medicine is a multi-faceted approach to healthcare in that it's proponents view the body as webbed connections, meaning all systems are inter-connected and attempt to identify conditions before they become full blown signs and symptoms.

Insulin resistance and other glycemic disorders are rampant in today's culture. The average American consumes about 2/3 cup of sugar a day. Diabetes is following close behind heart disease and cancer as a leading cause of death. It is evident that we as a culture need to re-evaluate our diets and lifestyles, as this is largely preventable. At the least, we can minimize the effects of diabetes and other glycemic disorders by eating less sugars and refined carbohydrates, eating more fruits and vegetables and by getting aerobic exercise several times a week. While insulin resistance is a pre-runner to diabetes, certain aspects are the same when compared. Prevention is key. If we eat foods that throw sugar directly

into our bloodstreams, our physiology has to adapt and increase insulin production. Too much sugar in the cells creates a caustic environment within the cell, so in return, the cells down-regulate insulin receptors on the cell. This leaves sugar in the bloodstream, which causes the pancreas to release more insulin in the blood (hyperinsulinemia). It's a viscious cycle, but there is hope.

Discussion

Insulin is a hormone produced from the Beta cells in the islets of Langerhans within the Pancreas. It's purpose is to lower the blood glucose level by accelerating the transport of glucose into cells, convert glucose into glycogen (a process called glucogenesis), and decreasing gluconeogenesis and glycogenolysis. Also, insulin increases lipogenesis and stimulates protein synthesis. Gluconeogenesis is forming glucose from lactic acid and certain amino acids. Glycogenolysis is the conversion of glycogen to glucose. Lipogenesis is the synthesis of fatty acids.²⁴ Excess sugar damages cells in your body through a process called Glycation, which works like the oxidation process. Imagine rust on metal, except, instead of oxygen being the offending molecule, it is glucose. Insulin is not supposed to be the primary blood sugar regulator. It is the liver and muscle's job to regulate any rise in blood sugar. However, when there is excess sugar, carbohydrates, or calories consumed, insulin is then required to lower the amount of sugar in the blood.

There are many ways to evaluate insulin sensitivity in the body. The conventional medical approach typically looks at blood laboratory tests. Functional medicine also takes into consideration other tests, such as the hair mineral analysis. *Hair mineral analysis* or hair tissue biopsy, can be used to determine if there is a glucose intolerance. There are many other things to look for besides insulin. The calcium/magnesium ratio, the sodium/potassium ratio, and many other mineral ratios can be indicative of

insulin resistance. Other than the pancreas and insulin, there are other minerals and glands that help to regulate glucose. Obviously, the pancreas is needed for secretion of insulin. Thyroid hormone is needed to burn the glucose once it is in the cells. The adrenals are another gland that influences glucose regulation. Cortisol converts amino acids and glycogen to glucose in order to raise glucose levels and adrenalin, also made in the adrenals, raises the blood sugar. Several minerals are responsible for glucose regulation. Zinc is needed to produce, release and extend the action of insulin. Chromium is needed for transport of insulin and to enable insulin molecules to attach to cell walls. Potassium is used to sensitize the tissues to thyroid hormone. Calcium is needed for insulin release. Calcium also affects cell permeability and cell membrane function. Magnesium inhibits insulin release and is used inside the cell for glucose regulation. Cadmium affects glucose intolerance in a negative way by interfering with zinc, which affects several cellular functions. Iron can be antagonistic to chromium and lead displaces calcium. Copper is also antagonistic to zinc and is needed for the electron chain. Copper is needed for the electron transport system to make more energy in the cell.

The hair mineral analysis shows trends instead of diagnoses. One of the more important ratios to investigate is the Calcium/Magnesium ratio. Since calcium is needed for insulin release and magnesium is needed to inhibit insulin release, a balance in these two minerals is imperative. The ideal ratio of calcium:magnesium is 6.67:1. In this case, magnesium supplementation may help improve insulin resistance, according to a study that included 52 overweight non-diabetic adults that were randomly assigned to receive either 365 mg of magnesium-aspartate-hydrochloride or a placebo daily for six months. The researcher found that insulin resistance was significantly improved in the magnesium supplemented with Magnesium with inflammatory markers and diabetes diagnoses in 4,497 individuals. This study found that the people who consumed the most magnesium were 47% less likely to develop diabetes than those who

consumed the least amount of magnesium. Higher magnesium levels were also linked to lower inflammatory markers and improvements in insulin resistance. ¹¹ *Magnesium* is needed for proper blood sugar metabolism, yet research suggests a substantial number of people are at risk for magnesium deficiency. Magnesium increases insulin sensitivity, making it easier for all the cells of your body to absorb and utilize glucose. There was a study that suggests that a diet rich in Magnesium may be linked to a decreased risk of diabetes. This study included 4,497 adult Americans, with an age range of between 18 and 30 that did not already have diabetes. At the start of this study and during the twenty year follow-up, the researchers evaluated the participant's magnesium intake and their inflammatory markers and recorded the number of diabetes diagnoses. The number of participants who developed diabetes by the end of the twenty year period was 300. This study concluded that the individuals that had the most magnesium in their diet, whether through food or supplementation, were 47 percent less likely to develop diabetes as compared to those that consumed less magnesium. Also, higher magnesium levels were linked to lower inflammatory markers and improvement in insulin resistance. ²⁰

A low sodium/potassium ratio is another indicative assessment to consider. Increased potassium is intimately linked to rising glucose due to the rise in glucocorticoids released from the adrenal glands. A low sodium/potassium ratio as found on a hair mineral analysis is also called sodium/potassium inversion. As the ratio drops below 2:1, it is considered a trend for glucose intolerance. On the other hand a low potassium hair mineral analysis would be more indicative of a hypoglycemic trend. Low hair potassium indicates low cortisol secretion. And, without the right amount of cortisol, then the body cannot adequately convert protein and glycogen into glucose to maintain blood sugar levels. This results in a chronic low blood sugar situation, also known as hypoglycemia. Potassium is also needed to sensitize cells to the thyroid hormone thyroxine. If there isn't enough potassium in the system, then the thyroid hormone becomes less

effective. Energy from the glucose isnt made in the cell and we have a situation similar to not having enough sugar in the cell.

Usually, a high calcium level is found with hypoglycemic individuals. Higher than 100 mg% is indicative of a high calcium level. It can reduce cell permeability, which the body may raise the blood sugar to attempt to push more glucose into the cells.

Low Chromium, Zinc or Manganese can cause sugar dysregulation as well. Chromium, an essential mineral, is one of the most critical nutrients for maintaining proper insulin levels, which in turn controls blood sugar levels and help the cells get the glucose they need to burn energy. Without chromium, insulin will not work properly, yet studies show that as many as 80% of Americans are not getting optimal levels of this mineral in their daily diet. Dietary supplements with Chromium has been shown to lower blood glucose concentrations and improve lipid profiles in diabetic patients. In a study at the University of Wyoming School of Pharmacy in the Division of Pharmaceutical Sciences and Center for Cardiovascular Research and Alternative Medicine, Chromium Supplementation to insulin resistant mice resulted in decreased serum insulin concentration. Glucose tolerance was significantly improved as evidenced by glucose disposal rate increase following an intraperitoneal glucose tolerance test, as compared to the control group. As well, chromium supplementation enhanced insulin-stimulated Akt phosphorylation and membrane-associated glucose transporter-4 in skeletal muscles of sucrose fed mice. The chromium that was used in the experiment was Chromium complex of D-phenylalanine. 5 In a double-blind, randomized study where there was found a moderate quality of methodology in subjects at high risk for diabetes, the participants were provided either placebos or 1000 mg/d of chromium picolinate for eight months. Insulin sensitivity was measured to determine insulin resistance. Compared with the control group, there was significant increase in insulin sensitivity for participants that took the Chromium picolinate. 6 Manganese is

needed for combustion of glucose within the mitochondria of the cell. Often times, Manganese will show up low on the hair mineral analysis. Levels should be between 0.03 and 0.12 mg%.

There are several blood tests available to determine the state of glucose balance in the blood. The A1C, glucose tolerance test, fasting glucose, the euglycemic clamp and HOMA-IR. The A1C test is a common blood test used to diagnose type diabetes mellitus (type 1 and type 2) and then gauge how well you have been managing your diabetes or glucose dysregulation. The A1C test is also called glycated hemoglobin, glycosylated hemoglobin, hemoglobin A1C and HbA1c. This test result reflects your average blood sugar level for the past two to three months. The A1C test measures what percentage of your hemoglobin, a protein in red blood cells that carries oxygen, is coated with sugar or glycated. The higher your A1C level, the more poorly your blood sugar is being controlled. And if you have previously diagnosed diabetes, the higher the A1C level, the higher your risk of diabetes complications. The cutoff percentage for diagnosis to be final for diabetes is \geq 7.0%, meaning at this level, it is not necessary to perform any other types of tests to confirm the diagnosis of diabetes. In a study in the Netherlands, the researchers found that a lower percentage would be more specific and sensitive at 5.8%. According to their study, this new cutoff would detect 72% of patients with newly diagnosed diabetes and 30% of individuals that are at high risk of developing diabetes (participants with intermediate hyperglycemia). $_{21}$

Fasting glucose test is a test that measures blood glucose in individuals who have not eaten anything for at least 8 hours. This test is most reliable when done in the morning. Fasting glucose levels of 100 to 125 mg/dL are above normal but not high enough to be called diabetes. This condition is called pre-

diabetes or IFG. People with IFG often have had insulin resistance for some time. They are much more likely to develop diabetes than people with normal blood glucose levels.

The glucose tolerance test, also known as the oral glucose tolerance test, measures your body's response to sugar. It can also be used to screen for type 2 diabetes. The glucose tolerance test identifies abnormalities in the way your body handles sugar after a meal, often before your fasting blood glucose level becomes abnormal. The glucose tolerance test is done in several parts. When the patient arrives at the doctor's office or lab, a member of their health care team will take a sample of blood by pricking the patient's fingertip or inserting a needle into a vein in their arm. This blood sample will be used to measure their fasting blood glucose level. They'll drink about 8 ounces (237 milliliters) of a syrupy glucose solution containing 2.6 ounces (75 grams) of sugar. Two hours later, the blood glucose level will be measured again. A blood glucose level between 140 and 199 mg/dL means glucose tolerance is not normal but is not high enough for a diagnosis of diabetes. This form of pre-diabetes is called IGT and, like IFG, it points toward a history of insulin resistance and a risk for developing diabetes.

Health care providers often use blood tests to determine whether a person has pre-diabetes but do not usually test for insulin resistance. Insulin resistance can be assessed by measuring the level of insulin in the blood. However, the test that most accurately measures insulin resistance, called the euglycemic clamp, is too costly and complicated to be used in most doctors' offices. The clamp is a research tool used by scientists to learn more about glucose metabolism. The homeostasis model assessment for insulin resistance (HOMA-IR) estimates insulin resistance from fasting plasma glucose and serum insulin levels ²⁵. There is good correlation between values of insulin resistance obtained using HOMA-IR and the euglycemic-hyperinsulinemic clamp method ²⁶, the gold standard test that is too costly and technically

demanding to be used in clinical practice. Given the combination of accuracy and ease of testing, HOMA-IR is considered an appropriate method for measurement of insulin resistance in epidemiologic studies. ₂₆

Some of the minerals that are beneficial to balance blood glucose was discussed earlier. There are also other vitamins, herbs and foods that help regulate glucose as well. Alpha-lipoic acid, also known as thioctic acid, is an antioxidant. This antioxidant nutrient improves the cells' response to insulin and can help stabilize blood sugar levels. Alpha lipoic acid has the unique ability to increase glucose uptake in the cell. ²⁸ Researchers at the Chia Nan University of Pharmacy and Science in Taiwan studied the effects of bitter melon on fat cell size and metabolism. In the experiment, there were four groups of rats. The first group was fed a high fat diet alone. The second group was fed a high fat diet supplemented with 5% lyophilized bitter melon and the third group was fed a high fat diet with 0.01% thiazolidinedione (TZD), which is a diabetic medication. The fourth group was the control. The were fed a low fat diet. An increase in insulin resistance and glucose intolerance was noted in the high fat group but not the High Fat with bitter melon or TZD. The number of large fat cells was significantly lower in the bitter melon and TZD group as compared to the High Fat group. However, the adipose tissue mass was lower in the bitter melon group than that of the TZD group, given evidence that bitter melon might reduce new fat cell growth in the existing fat tissue. Results also indicated that the bitter melon can reduce insulin resistance as well as the thiazolidinedione. ⁸

Gymnema Sylvestra an herb from India, has a 2000 year history of being used in Auryvedic medicine for the use of controlling blood sugar. In a clinical study, the effectiveness of Gymnema was exhibited when Gymnema sylvestra (GS) was supplemented in addition to conventional oral hypoglycemic agents. One group of 22 patients with Type II diabetes received the addition of GS to their oral hypoglycemic agents and the other group of 25 used only the conventional oral hypoglycemic agents. The study was for a period of 18-20 months. A statistically significant reduction was evidenced by the patients'

mean fasting blood glucose by approximately 50 mg% after 18 months and their mean HbA1c decreased from a baseline of 11.9 % to 8.34% in the participants that received the supplementation of GS. In these individuals, the dosage of oral hypoglycemic agents had to be reduced in order to avoid hypoglycemia and 5 of the 22 participants were able to completely get off of the conventional oral hypoglycemic agents and blood glucose balanced was achieved with the GS only. ₁₃ In another study by Shanmugasundaram et al., both the normal rats and the rats treated with streptomyocin were treated with either a 50% ethanolic extract of gymnema leaves (GS₃ at 20 mg/day/rat), a purified residue of GS₃ (GS₄, 20mg/day/rat), or no intervention for 95 days. Both of the treated diabetic rats showed a 30% increase in pancreatic weight, as well as an increase in the number of islets and number of beta cells per islet. This regeneration of pancreatic cells resulted in complete glucose homeostasis within 60 days in the GS₃ group and 20 days in the GS₄ group. ₁₄ As a supplement, Gymnema is an effective addition to a health regimen that focuses on glucose tolerance. It not only helps with maintaining balanced blood glucose, it also assists in controlling weight, hypertension, lowering inflammatory markers and atherogenic lipid indices, and improving metabolic control. ₁₅

Barberry. In one study, berberine improved insulin resistance and liver glycogen levels similar to metformin when given to rats that were fed a high fat diet. ₁₈ Similarly, in another study, rats that had alloxan-induced diabetes mellitus were treated with berberine and the result was that the rats had significantly lower blood sugar than the control rats. ₁₉

Fenugreek. Trigonella foenum-graecum, commonly known as fenugreek, is a plant that has been extensively used as a source of anti-diabetic compounds from its leaf and seeds extracts. Preliminary human trials and animal experiments suggest possible hypoglycemic and anti-hyperlipedemic properties of fenugreek seed powder that is taken orally. Results from one study show that the action of fenugreek for

lowering blood glucose levels is almost comparable to the effect of insulin. It also inhibits the activities of αamylase and sucrose. Combination with trace metal showed that vanadium had additive effects and manganese had additive effects with insulin on in vitro system in control and diabetic animals of young and old ages using adipose tissue. The Fenugreek and vanadium effects were studied in a number of tissues including liver, kidney, brain peripheral nerve, heart, red blood cells and skeletal muscle. Adding Fenugreek to vanadium significantly removed the toxicity of vanadium when used to reduce blood sugar levels. Administration of the various combinations of the anti-diabetic compounds to diabetic animals was found to reverse most of the diabetic effects studied at physiological, biochemical and molecular levels.₂₇ Vanadium has an insulin-like effect, helping to promote normal insulin function by driving glucose into the cells, also decreasing fasting blood sugar levels.

Hydroxycitric Acid. According to a study at the College of Pharmacy at the University of Houston, Hydroxycitric Acid from Garcinia cambogia could be used to treat obesity and obesity related complications, such as insulin resistance. Researchers investigated the effect of hydroxycitric acid (HCA-SX) on inflammation, oxidative stress and insulin resistance in developing obese Zucker rats that were supplemented with a control and HCA-SX in their drinking water for a period of seven weeks.The hydroxycitric acid in the study is a calcium/potassium salt of (-) hydroxycitric acid derived from the dried fruit rind of the plant Garcinia cambogia, and it is commonly consumed in weight loss products. Researchers noted that insulin resistance did not develop in the rats that were supplemented with hydroxycitric acid as compared to the control group. 9

Vitamin K. In one study, three hundred fifty-five non-diabetic men and women participants between the ages of 60 and 80, were randomly divided into two separate groups. One group received 500 micrograms of Vitamin K1 (phylloquinone), five times the Adequate Intake that is recommended by the

Institute of Medicine's Food and Nutrition Board, daily for 36 months. They also took calcium and Vitamin D. The contol group only took the calcium and the Vitamin D. The men in the group faired better than the women in the group. The men in the Vitamin K group had improved insulin resistance, however, the women had no significant change. The researchers suggested that the female participants had a higher prevalence of obesity and this may have played a role in the poor results for the women's group. 10

Cinnamon. Cinnamon has long been known to help increase insulin sensitivity. The active ingredient in cinnamon, hydroxychalcone, affects insulin receptors that help promote glucose uptake into the cells and help promote glycogen synthesis. A Diabetes Care study, in 2003, found that cinnamon was found to improve glucose and lipids in diabetic individuals. In this study, sixty participants exhibiting Type II Diabetes, taking sulfonylurea (glyburide) were given cinnamon or a placebo for fourty days. The participants fasting blood glucose declined by 18-29 percent after the fourty days. In addition, the participants fasting glucose was still lower than their baseline twenty days after that had stopped taking the cinnamon. 7

Aerobic Exercise. Research shows that physical activity greatly effects blood sugar regulation. Researchers at the Harvard School of Public Health in Boston found that a brisk daily walk for just one hour every day was just as effective as running or jogging and that it cut women's risks of developing Type II Diabetes Mellitis down by sixty percent. ₁₂ A study was done to acertain the benefits of resistance training or aerobic training in improving insulin sensitivity. A 12-week exercise program of either resistance or aerobic activity showed improved insulin sensitivity in overweight adolescents. Aerobic exercise decreased both body weight and BMI, and it was noted that this group also had a significant reduction in muscle mass when compared to the Diet Only group.₂₈

Anti-Inflammatory Diet. The anti-inflammatory diet consists of foods that will create antiinflammatory prostagalndis rather than pro-inflammatory prostaglandins. Prostaglandins made from dietary fats have many functions; for example, they are involved in vasodilation, bronchodilation, inflammatory reactions and the regulation of cell proliferation. The main idea of an anti-inflammatory diet is to avoid "bad" fats and to consume "good" fats. Bad fats are polyunsaturated and partially hydrogenated fats and oils. These fats lead to the production of pro-inflammatory prostaglandins and should be eliminated from the diet. These fats are found in most pocessed foods and are hard to avoid. Trans-fats should also be avoided. These are most often found in shortening and margarine. Olive oil is a great alternative to these. Good fats include omega-3 fatty acids, found mostly in fish of cold water origin. These fish include mackerel, salmon, sardines, anchovies and herring. Omega-3 fatty acids are also found in walnuts, Brazil nuts, almonds, and pumpkin seeds. Other foods that have anti-inflammatory properties include fruits, like blackberries, strawberries, kiwi, peaches, cantaloupe, apples, and carrots. Also, vegetables, such as, squash, sweet potato, spinach, collard greens, broccoli, cabbage and brussel sprouts. Some studies suggest a link between the inflammatory process and insulin resistance, so following the anti-inflammatory diet may help with blood glucose regulation. 16 The diet also suggests to avoid man-made sweetners like high-fructose corn syrup, corn syrup, dextrose and malto dextrose. Which all increase inflammation and increase insulin production.

Low Carbohydrate Diet. In a study at Pennsylvania State University, researchers investigated the effects of carbohydrate-restricted diets on weight loss and body fat reduction and the associated changes in circulating leptin, insulin, ghrelin, and cholecystokinin concentration in overweight patients with metabolic syndrome. The results of the study showed a decrease in body mass index, body weight and total body

fight percentage. Also, plasma fasting insulin and leptin concentrations were significantly lower than baseline concentrations. 17

Conclusion

The literature suggests that there are several ways of evaluating and treating insulin resistance in a balanced way that is specific to each patient. The patient should be evaluated according to their individual imbalances, whether that be with a mineral, heavy metal toxicity, carbohydrate ratio ingestion or lack of exercise. It is best to find the specific cause or causes of the glucose dysregulation problem, so that the clinician can best proceed with a more definitive course of treatment. The best test for insulin resistance is the euglycemic hyperinsulinemia clamp method, however, that test is expensive. The next best way to determine a patient's insulin sensitivity is to do a (HOMA-IR) homeostasis model assessment for insulin resistance. Once the patient has been deemed insulin resistant, they may go about correcting their situation by any number of the following ways. While a combination of weight loss and exercise is considered the best treatment, it is important to consider the subtle imbalances that may be lurking in the body. Depending on their particular imbalance, they may supplement with minerals, herbs, or vitamins. It has been shown that a low carbohydrate, anti-inflammatory diet may be needed as well when correcting sugar regulating dysfunctions.

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