**Insulin Resistance Protocol / Evidence**

Below are the nutraceuticals we find most beneficial for insulin resistance/metabolic syndrome as well as adrenal support; Please don't hesitate to reach out for any additional questions or support!

**What is Insulin Resistance?**

Insulin resistance is a condition in which the body's cells become resistant to the effects of insulin, a hormone produced by the pancreas that regulates blood sugar levels. In normal conditions, insulin helps glucose (sugar) in the blood enter cells, where it is used as energy or stored for later use. However, in insulin resistance, the cells become less responsive to insulin's actions, leading to increased levels of glucose in the blood.

The pathophysiology of insulin resistance is complex and involves multiple mechanisms. One major factor is the accumulation of lipids (fats) in the cells, particularly in muscle and liver cells. This leads to a state of "lipotoxicity," which impairs insulin signaling pathways and reduces glucose uptake.

Another key contributor to insulin resistance is chronic inflammation. Inflammatory cytokines, such as TNF-alpha and IL-6, interfere with insulin signaling and contribute to insulin resistance. Obesity is also associated with increased inflammation and is a major risk factor for insulin resistance.

Insulin resistance can also be caused by genetic factors, including mutations in genes involved in insulin signaling pathways. Additionally, aging is associated with decreased insulin sensitivity, as well as other metabolic changes that contribute to insulin resistance.

Over time, insulin resistance can lead to further complications, including impaired glucose tolerance, type 2 diabetes, and cardiovascular disease. These conditions are often accompanied by additional metabolic abnormalities, such as dyslipidemia (abnormal blood lipid levels) and hypertension (high blood pressure).

As insulin resistance progresses, the pancreas may compensate by producing more insulin to try to lower blood glucose levels. However, over time, the pancreas may become exhausted and unable to keep up with the demand for insulin, leading to type 2 diabetes.

Insulin resistance is also associated with other metabolic abnormalities, including high levels of triglycerides and low levels of HDL cholesterol, a condition known as dyslipidemia. These abnormalities increase the risk of cardiovascular disease, which is the leading cause of death among people with type 2 diabetes.

In addition to obesity, other factors that contribute to insulin resistance include a sedentary lifestyle, a diet high in processed foods and sugar, and certain medications, such as glucocorticoids. Insulin resistance is also associated with other health conditions, such as polycystic ovary syndrome (PCOS), nonalcoholic fatty liver disease (NAFLD), and sleep apnea.

Treatment for insulin resistance typically involves lifestyle changes, such as a healthy diet and regular exercise, along with medications such as GLP-1 RA (i.e. semaglutide, tirzepatide, etc.), which helps improve insulin sensitivity and reduce the risk of complications associated with insulin resistance. Managing insulin resistance is important for reducing the risk of complications associated with type 2 diabetes and cardiovascular disease.

Insulin resistance can affect the balance of several hormones in the body, which can contribute to a range of health issues. One way that insulin resistance affects hormones is by disrupting the function of the hypothalamic-pituitary-adrenal (HPA) axis, which is a complex system that regulates the body's stress response.

In insulin resistance, the body produces more cortisol, a stress hormone that can lead to a range of negative effects, including weight gain, increased appetite, and decreased insulin sensitivity. High cortisol levels can also contribute to the development of conditions such as depression, anxiety, and sleep disorders.

Insulin resistance can also affect the balance of sex hormones, such as estrogen and testosterone. In women, insulin resistance can lead to a condition called polycystic ovary syndrome (PCOS), which is characterized by high levels of androgens (male hormones) and irregular menstrual cycles. PCOS can also contribute to infertility, acne, and excess hair growth.

In men, insulin resistance can lead to lower testosterone levels, which can contribute to decreased libido, erectile dysfunction, and reduced muscle mass. Insulin resistance can also affect the balance of other hormones, such as leptin and ghrelin, which regulate appetite and satiety.

Overall, insulin resistance can have a profound effect on hormone balance, which can contribute to a range of health issues. By improving insulin sensitivity through lifestyle changes or medication, it may be possible to restore hormone balance and improve overall health.

## Insulin Resistance - Evidence

### ALA (Alpha Lipoic Acid) and Atherosclerosis

Oxidative stress is considered to be the primary cause in many cardiovascular diseases, including atherosclerosis.[42] As we age, oxidative stress increases through an increase in the production of reactive oxygen species and/or a decrease in the body's antioxidant defenses. This increase in oxidative stress is paralleled by an increase in cardiovascular conditions like atherosclerosis. Research demonstrates that antioxidants help to decrease the incidence of atherosclerosis. ALA exerts potent antioxidant effects on the body and has been studied in experimental models for its ability to prevent and reverse atherosclerosis.

In one study, Watanabe heritable hyperlipidemic rabbits were fed with high cholesterol chow for 6 weeks and then randomized to receive either high cholesterol diet alone or high cholesterol diet combined with 20 mg/kg/day of ALA for 12 weeks.[43] At the end of the 12 weeks, researchers found that ALA decreased body weight by 15 ± 5% without alterations in lipid parameters and reduced atherosclerotic plaque in the abdominal aorta with morphological analysis revealing reduced lipid and inflammatory cell content.

Furthermore, ALA improved vascular reactivity (as revealed by decreased constriction to angiotensin II and increased relaxation to acetylcholine and insulin), inhibited NF-κB activation, and decreased oxidative stress and expression of key adhesion molecules in the vasculature.
An unrelated study demonstrated the cardioprotective effects of ALA. Eighteen adult male New Zealand White rabbits were randomly assigned to three groups for 10 weeks. One group was fed with normal chow (control group), one was fed with a 1% high cholesterol diet to induce hypercholesterolemia, and the third group was fed a 1% high cholesterol diet plus 4.2 mg/body weight of ALA. At the end of the study, blood total cholesterol (TCHOL) and low- density lipoprotein (LDL) levels were found to be significantly lower in the ALA group compared to that of the group that consumed a high cholesterol diet alone. The ALA group also had less atherosclerotic plaque in their aortas than the group that consumed a high cholesterol diet alone, leading researchers to conclude that, apart from its antioxidant activity, ALA may also exert a lipid-lowering effect on TCHOL and LDL levels and may reduce atherosclerosis formation in rabbits fed a high cholesterol diet.
A similarly designed study conducted on streptozotocin-induced diabetic mice models revealed that ALA completely prevented the increase in TCHOL, atherosclerotic lesions, and the general decline in health typically observed with diabetes, suggesting that ALA is a promising protective agent for reducing cardiovascular complications of diabetes.[44]
Studies evaluating the efficacy of ALA in the prevention/treatment of atherosclerosis are limited to experimental data; however, the safety of the supplement and the potential benefits make it a promising intervention in primary care and cardiology settings.

**ALA and Chronic Fatigue Syndrome**

Chronic fatigue syndrome (CFS), also referred to as myalgic encephalomyelitis, is an illness characterized by debilitating and relapsing fatigue and often accompanied by neuropsychiatric concerns, such as depression, irritability, sleep disorders, autonomic symptoms and neurocognitive defects, as well as physiosomatic concerns, such as malaise, hyperalgesia, irritable bowel, and muscle pain and tension. Oxidative stress[24-25] and inflammation[25] play important roles in the pathogenesis of CFS. In fact, some have suggested that CFS should be renamed in order to better reflect the oxidative and inflammatory nature of the condition.[26] Some have also suggested that mitochondrial dysfunction may play a role in the condition.[27]
Researchers have studied ALA in the treatment of CFS because of its antioxidant and anti-inflammatory properties, as well as its role in mitochondrial function.
When administered orally, ALA is rarely present in tissues above micromolar levels and is therefore unlikely to function as a primary cellular antioxidant.[19] Instead, its potent antioxidant properties appear to be attributable to the fact that ALA increases cellular glutathione levels by regulating glutathione synthesis and ameliorating oxidative stress.[20]
ALA may exert its anti-inflammatory effects by scavenging free radicals and down- regulating pro-inflammatory redox-sensitive signal transduction processes including nuclear factor kappa B translocation, leading to decreased release of other free radicals and cytotoxic cytokines.[21-22]
Evidence implicates mitochondrial dysfunction, impaired oxidative phosphorylation and abnormally high lactate levels in the pathophysiology of CFS.[25] ALA acts as a critical cofactor in mitochondrial alpha-ketoacid dehydrogenases, including pyruvate dehydrogenase. As a result, itis important in

mitochondrial, oxidative-decarboxylation reactions and plays a critical role in mitochondrial activity and energy metabolism.[28] Furthermore, supplementation with ALA has been demonstrated to lead to a decrease in abnormally elevated lactate levels,[4] likely as a result of its role in stabilizing and regulating pyruvate dehydrogenase and other mitochondrial 2- ketoacid dehydrogenase complexes.[29]
Although there are no randomized controlled trials using ALA in the treatment of chronic fatigue syndrome, when we consider its widespread use as a safe nutrient with the ability to reduce oxidative stress, decrease inflammation, and support mitochondrial function, its use in addressing chronic fatigue syndrome appears to be justified.

**ALA and Type-2 Diabetes**

Type-2 diabetes is associated with high levels of oxidative stress.[1] Specifically, diabetes impairs endothelial nitric oxide synthase activity and increases the production of reactive oxygen species, thus resulting in diminished nitric oxide bioavailability and increased oxidative stress.[2] Alpha-lipoic acid, a disulfide compound that is produced in small quantities in cells and serves as an antioxidant at pharmacological doses, has been shown to improve insulin sensitivity in type-2 diabetic patients. In addition to its antioxidant properties, it is also beneficial in cases of diabetes because of its anti-inflammatory and hypoglycemic[4] properties.
In one recent open-label study in which lean and obese individuals with type-2 diabetes were administered 600 mg ALA by mouth, twice per day for four weeks, treatment with ALA was associated with increased glucose effectiveness in both lean and obese diabetics relative to non-diabetic lean and obese controls.[4] Lean diabetic patients were also found to have a higher degree of insulin sensitivity and lower fasting glucose. Furthermore, after ALA treatment, lactate and pyruvate before and after glucose loading were approximately 45% lower in both obese and lean diabetics, leading researchers to conclude that treatment with ALA prevents hyperglycemia- induced increments of serum lactate and pyruvate levels and increases glucose sensitivity.
As the result of another study, researchers concluded that oral treatment with 800 mg/day for 4 months may improve cardiac autonomic dysfunction in type-2 diabetics.[5]
Intravenous administration of ALA has also been shown to be beneficial in type-2 diabetes. In a small, randomized, controlled trial, 13 patients received either 1000 mg ALA or normal saline.[6] Both groups were comparable in age, BMI, and duration of diabetes. They also had similar degrees of insulin resistance at baseline. After administration of ALA, patients experienced a significant increase of insulin-stimulated glucose disposal. Metabolic clearance rate for glucose rose by about 50% in the treatment group, while the control group did not experience any significant change. Similar results, specifically a 30% increase in insulin-stimulated glucose disposal, were demonstrated in an uncontrolled, pilot trial that administered 500 mg ALA intravenously per day over a 10-day period.[7]
In another study, while both oral and intravenous administration of ALA led to improvements in insulin sensitivity, the improvements associated with oral administration were minimal (about 20%) compared to the improvements seen with intravenous administration. The intravenous route of administration remained superior, despite higher doses of oral ALA (up to 1800 mg) and longer treatment time (30 days oral vs. 10 days IV).[8-9]

**Effects of Polyphenols on Insulin Resistance**

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Abstract: Insulin resistance (IR) is apparent when tissues responsible for clearing glucose from the blood, such as adipose and muscle, do not respond properly to appropriate signals. IR is estimated based on fasting blood glucose and insulin, but some measures also incorporate an oral glucose challenge. Certain (poly)phenols, as supplements or in foods, can improve insulin resistance by several mechanisms including lowering postprandial glucose, modulating glucose transport, affecting insulin signalling pathways, and by protecting against damage to insulin-secreting pancreatic β-cells. As shown by intervention studies on volunteers, the most promising candidates for improving insulin resistance are (−)-epicatechin, (−)-epicatechin-containing foods and anthocyanins. It is possible that quercetin and phenolic acids may also be active, but data from intervention studies are mixed. Longer term and especially dose-response studies on mildly insulin resistant participants are required to establish the extent to which (poly)phenols and (poly)phenol-rich foods may improve insulin resistance in compromised groups.

**Effects of coenzyme Q10 supplementation on glycemic control: A GRADE-assessed systematic review and dose-response meta-analysis of randomized controlled trials**

Interpretation: CoQ10 supplementation has beneficial effects on glycemic control, especially in diabetes, and 100-200 mg/day of CoQ10 could achieve the greatest benefit, which could provide a basis for the dietary guidelines of CoQ10 in patients with glycemic disorders.