Insulin Resistance

Insulin resistance (IR) is a very common condition. It is very serious in that it can greatly contribute to the development of chronic illness including but not limited to cardiovascular disease, renal issues, and other forms of disease. Insulin inhibits activity of the vagus nerve motor nucleus, therefore causing individuals with IR to have more systemic inflammation, more IL-6 mediated autoimmune flare activation, more SIBO and gastroparesis, etc. ***(Kimura, Cell Reports 2016).*** Below is a summary of the immunology behind IR and how it affects individuals with it.

The goal in the body is to make enough insulin and for the receptors for insulin to work properly. Insulin production is impaired when pancreatic beta cells are being destroyed, either by NLRP3 inflammasome mediated destruction, or by autoimmune destruction. Insulin receptors are downregulated by inflammation ***(de Luca, FEBS lett, 2007)*** so those with chronic inflammation are more susceptible to developing IR. These factors are all inherently immunological, so they're influenced by other factors in the persons immunological map and they also affect other factors within that. Let's unpack the interconnections.

The first consideration is identification. Blood work is very important to confirm a possible issue. That being said, waist/hip ratio and overall body habitus, along with dietary practices and related information from the persons history will often track closely with lab outcomes. Still, part of the point of running labs is to be available for the surprises that appear. Hemoglobin A1c is the gold standard test. It measures the extent to which glucose in the blood has been too high, such that it attaches to hemoglobin (glycosylation). RBC's live four months, so you're looking at a four month reference frame. Don't measure HA1c too often, as you'll just be measuring the same population of RBC's. In some folks, the HA1c isn't high, despite the IR. Because of this, a test called 1,5 anhydroglucitol (1,5 AG) has been developed and is referred to as the glycomark test. 1,5 AG is lost in the glomerulus and recaptured in the distal renal tubule, but that recapture is blocked by elevated blood glucose, so folks with high blood glucose lose 1,5 AG in the urine, and the serum 1,5 AG goes down. So, low values here suggest glucose elevation (short term) even with normal HA1c.

Not to get too technical but In addition to other markers of glucose regulation, it's worth mentioning that there is research showing that **lowered levels of alpha-1-antitrypsin (AAT) are associated with T1D.** ***(Kalis, Islets 2010)*** AAT has also been proposed as a treatment for T1D and T2D. Ask your doctor or practitioner about this and what it means if you believe you have IR.

Once you've established that glycemic reorganization (aka you have IR) is necessary, clearly diet will play a central role. There are plenty of resources on this site and elsewhere that touch on how to eat to support your blood sugar levels so we won't touch on that here (if you have questions about diet, post them to the forums!). One consideration about diet from an immunological point of view is that exogenous sources of dietary ketones can be inflammasome activators ***(Nudorf, Mol Nutr Food Res. 2019).*** That suggests a ketogenic diet, but not ingestion of exogenous ketones, would

be worthy of consideration. This might be especially important in people for whom pancreatic beta cell death is driven by the NLRP3 inflammasome.

Another dietary consideration is that different people may respond to the same food pattern with different glycemic responses, based on differences between patients with respect to their microbiome. This makes the use of a continuous glucose monitor potentially important, so the patient can identify actual glycemic impacts of various food strategies.

In addition to food intake, exercise is another important topic not covered in this Clinical Pearl. Patients with greater amounts of muscle mass will have a better chance of doing efficient work in converting glucose to muscle glycogen as a storage form than those with age related or other sarcopenic states.

If you are experiencing apoptosis (programmed cell death) of pancreatic beta cells, this could be driven by an autoimmune process. Pancreatic autoimmunity can be measured by testing four antibodies. All of them need to be measured. They are antibodies to: Insulin, islet cells, GAD65, ZnT8. One could be high and the others not high, so it's not enough to just run one or two. The paper by Notkins ***(Scientific American '07)*** was a milestone when it came out. In it, Notkins discusses predictive antibodies, where the point is that **an autoimmune process could be developing in a person who does not yet meet the diagnostic criteria for a disease but for whom the autoimmune process is developing.** The Scientific American paper discusses the increasing level of risk of developing T1D associated with having 1, 2, 3, or more pancreatic antibodies.

So, even if you don't meet diagnostic criteria for T1D, the presence of antibodies tells you that you need to focus on the process in a way that includes understanding and addressing the autoimmune process, in order to dampen or halt the potential progression into a full manifestation of autoimmune disease. A substantial percentage of people with type 2 diabetes (T2D) also turn out to have antibody elevation, so they either already have type 1 diabetes (T1D) or they are on their way to developing it. **The death of pancreatic beta cells could also be driven by the biology of inflammasomes.** The paper by ***Strowig, et al. (Nature 2012)*** discusses the role of the NLRP3 inflammasome in the biology of obesity, insulin resistance, and pancreatic beta cell death. It is crucial to work with a practitioner who understands all this and who can help you in supporting your blood glucose and insulin levels.

Supplemental Considerations Beyond Food Changes:

The below information is shared by Dr. Yanuck.

- Berberine – 1 gram per meal at breakfast and lunch (if taken later than 4pm, can interfere with sleep, since it drives ATP production). Berberine turns on AMPK, which drives metabolic activation, ATP production (less fatigue), and AMPK inhibits inflammasome formation. Berberine has been shown to be as effective as metformin in T2D patients. ***(Yin, Metabolism 2008)*** and has been shown to be effective in a meta-analysis of human diabetes trials ***(Guo, Oxid Med Cell Longev 2021).***
- Reishi – Reishi (also called ganoderma) is a mushroom that downregulates protein tyrosine phosphatase 1b (PTP1b) ***(Yu, ACS Omega 2021).*** When insulin stimulates the insulin

receptor, the insulin receptor signals for an intracellular response that is a cascade of activities that cause glucose transporters (GLUT-4 transporters) to embed in the cell membrane, causing glucose transport into the cell. The duration of activation of the intracellular response (how long the insulin receptor keeps signaling) is different in different people. Inside the cell is the PTP1b enzyme, which turns the receptor off. If PTP1b is too efficient, the receptor turns off too soon, leading to what looks like insulin resistance (driven by inflammation) but isn't classical insulin resistance. And of course, you don't have to choose. You can have regular insulin resistance (driven by inflammation) and also have overactive PTP1b. Reishi downregulates PTP1b. In those for whom this is a factor, first morning glucose will be lower with reishi given at or near bedtime. Here's how to figure out if PTP1b is too active: first get a week worth of baseline data about first a.m. blood sugar. Next, take ganoderma (reishi) at bedtime, start with 0.5 gram. After five nights, raise to 1 gram. Does it lower first morning glucose? Check on five nights/mornings. Then try 2 grams. Same question. If the ganoderma does lower a.m. glucose, give the amount that worked 30 minutes before each meal, to keep insulin receptors turned on longer.

- Resveratrol – According to ***Um, et al. (Diabetes, 2010),*** resveratrol increases metabolic rate, insulin sensitivity, mitochondrial biogenesis, and physical endurance and reduces fat accumulation. This effect depended upon AMPK, so there is a synergy between resveratrol and berberine, such that the useful effect of resveratrol is amplified by berberine. At least 200mg bid would be a suitable dose to consider.

Regarding inflammasome biology, the following are worthy of consideration. Doses might need to be higher, depending upon the patient:

- Curcumin – 1 gram bid or tid.
- Nicotinamide riboside (a SIRT2 promoter) – 800mg to 1 gram bid
- Tart cherry juice or a tart cherry extract – 6 oz of juice or a substantial equivalent extract
- Pure Encapsulations Liposomal vitamin C liquid – 500mg daily

ALWAYS CHECK WITH YOUR RPACTITIONER BEFORE SUPPLEMENTING!

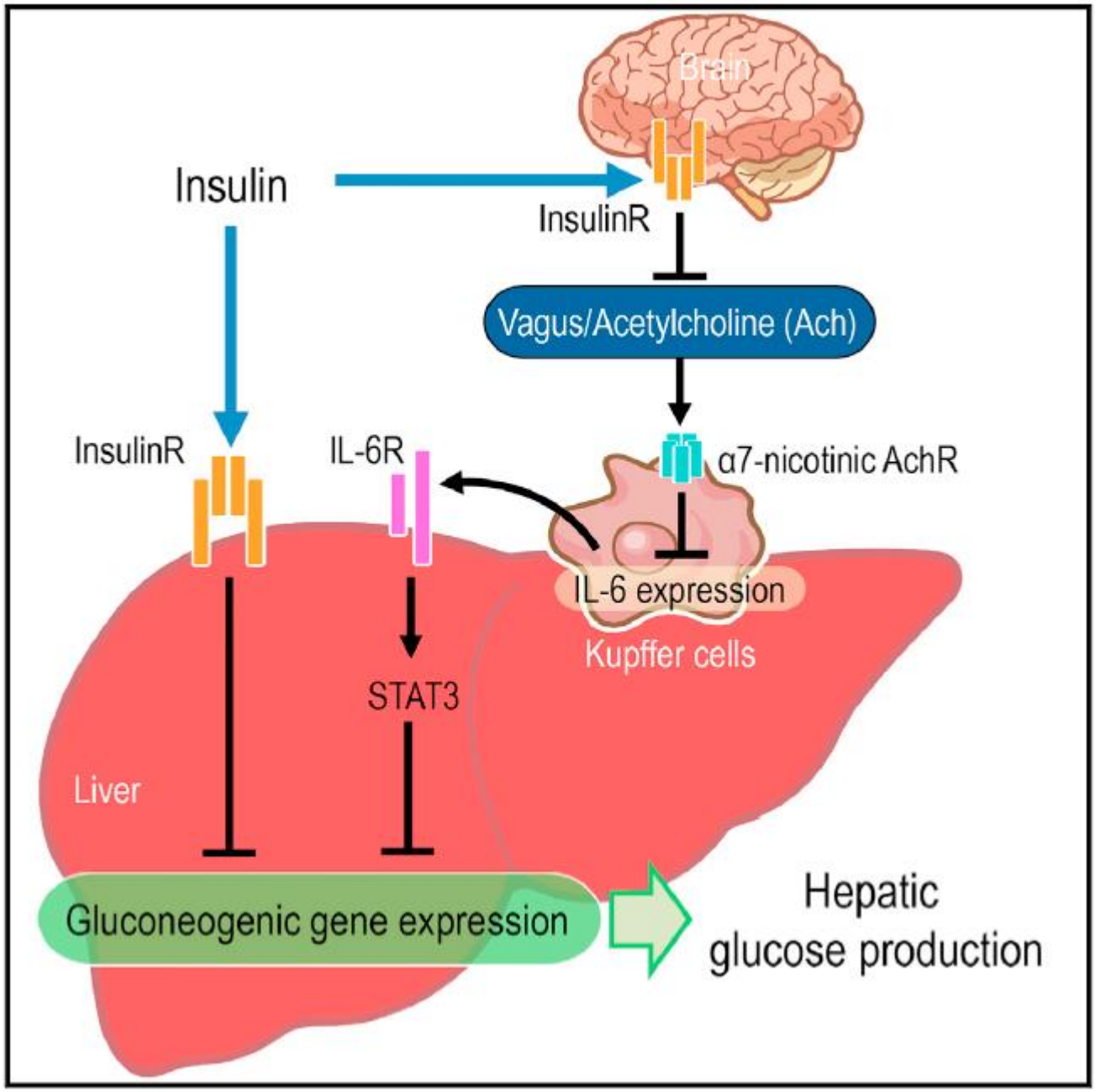
Chromium and vanadium are trace minerals essential for blood sugar regulation. These need to be supplemented at adequately robust doses, typically 250-500mcg qd for each.

There are other nutritional supports, like gymnema or bitter melon, that might be considered. However, the research support for these isn't as strong. Nonetheless, some people might respond well to supplementation with one or another of the more extended group. I tend to stay away from cinnamon, due to its histaminic effects.

The Research

Central Insulin Action Activates Kupffer Cells by Suppressing Hepatic Vagal Activation via the Nicotinic Alpha 7 Acetylcholine Receptor
Cell Rep. 2016 Mar 15;14(10):2362-74. Kimura K, Tanida M, Nagata N, et al.
Abstract
"Central insulin action activates hepatic IL-6/STAT3 signaling, which suppresses the gene expression of hepatic gluconeogenic enzymes. The vagus nerve plays an important role in this centrally mediated hepatic response; however, the precise mechanism underlying this brain-liver interaction is unclear. Here, we present our

findings that **the vagus nerve suppresses hepatic IL-6/STAT3 signaling via α7-nicotinic acetylcholine receptors (α7-nAchR) on Kupffer cells,** and that central insulin action activates hepatic IL-6/STAT3 signaling by suppressing vagal activity. Indeed, central insulin-mediated hepatic IL-6/STAT3 activation and gluconeogenic gene suppression were impeded in mice with hepatic vagotomy, pharmacological cholinergic blockade, or α7-nAchR deficiency. In high-fat diet-induced obese and insulin-resistant mice, control of the vagus nerve by central insulin action was disturbed, inducing a persistent increase of inflammatory cytokines. These findings suggest that dysregulation of the α7-nAchR-mediated control of Kupffer cells by central insulin action may affect the pathogenesis of chronic hepatic inflammation in obesity."



Inflammation and insulin resistance

FEBS Lett. 2008 Jan 9;582(1):97-105. De Luca C, Olefsky JM.

Abstract

“Obesity-induced chronic inflammation is a key component in the pathogenesis of insulin resistance and the Metabolic syndrome. In this review, we focus on the interconnection between obesity, inflammation and insulin resistance. **Pro-inflammatory cytokines can cause insulin resistance in adipose tissue, skeletal muscle and liver by inhibiting insulin signal transduction.** The sources of cytokines in insulin resistant states are the insulin target tissue themselves, primarily fat and liver, but to a larger extent the activated tissue resident macrophages. While the initiating factors of this inflammatory response remain to be fully determined, chronic inflammation in these tissues could cause localized insulin resistance via autocrine/paracrine cytokine signaling and systemic insulin resistance via endocrine cytokine signaling all of which contribute to the abnormal metabolic state.