Insulin Resistance Application Guide

Clinical Context

Dysglycemia, typically characterized by insulin resistance (IR) isn't typically thought of as an immunological phenomenon. There are several ways that IR can play a key role in your patient's immunological dysfunction.

1. IR leads to hyperglycemia. Hyperglycemia drives glucose attachment to protein, termed glycation. But hemoglobin isn't the only protein that can become glycated. Antibody glycation makes the antibodies more aggressive in attaching to their targets. If a patient's blood sugar gets dysregulated, the higher blood sugar levels can drive greater autoimmune attack and more tissue damage. If the debris from tissue damage instigates epitope spreading, the extent of autoimmune activation can be increased for the long term.

IR > hyperglycemia > ↑ antibody glycation > ↑ antibody binding to self-tissue targets > ↑ autoimmune flare activation

2. Glycation generates advanced glycation end products (AGEs), which drive NFkB-mediated inflammatory activation.

3. Hyperglycemia drives mitochondrial over-fueling, such that the mitochondria are damaged, generate more ROS, which drives NFkB activation. The ROS also drives multi-receptor resistance, including T3 receptor downregulation and insulin receptor downregulation. The insulin receptor downregulation worsens the hyperglycemia, yielding a loop. For more on this, look at the videos in Module 21 on neuropathy.

IR > hyperglycemia > mitochondrial over-fueling > ROS > IR (loop)

4. The ROS generated by mitochondrial over-fueling inhibits autophagy and depletes glutathione (GSH). Low GSH yields poor Th1 response, diminishing interferon gamma (IFNg) required for autophagy. And the NLRP3 inflammasome activation driven by hyperglycemia pushes T cells into Th2 polarization, further inhibiting Th1-mediated activation of autophagy. So, in three ways, the escalation of ROS and NLRP3 by hyperglycemia yields poor autophagy. And, when insulin production is low, so is c-peptide production. C-peptide and autophagy are two mechanisms by which neurons are repaired, so declining integrity of autophagy is a contributor to loss of CNS integrity. This is perhaps why dementia is described as type 3 diabetes.

5. Inflammation is often a key driver of IR. And IR drives hyperglycemia. Hyperglycemia inhibits SIRT2, allowing NLRP3 inflammasome activation, greatly increasing inflammatory activation. (loop) What's worse, NLRP3 inflammasome activation drives pancreatic beta cell loss. As beta cell numbers decline, so do insulin levels, yielding more hyperglycemia.

Inflammation > IR > hyperglycemia > ↓ SIRT2 > ↑ NLRP3 > Inflammation (loop) *and* NLRP3 > beta cell loss > low insulin > hyperglycemia (loop)

Inflammasome activation sharpens the pro-inflammatory cytokine push, causing cells to pour out copious amounts of IL-1β and IL-18, both of which attract neutrophils into tissue. The NLRP3 inflammasome is a known driver of atherosclerosis, adipocyte fat storage, and death of pancreatic beta cells. SIRT2 inhibition (by uric acid, low systemic pH, hyperglycemia, high cholesterol, low potassium, etc.) allows NLRP3 inflammasome assembly, driving the outpouring of inflammatory cytokines from the cell. (For more on inflammasomes, see Module 8 Videos 7 & 8). If NLRP3 inflammasome activation runs forward and causes death of enough beta cells, he won't be able to keep making enough insulin to keep his blood glucose down. If that happens, the patient can get a feed-forward loop, where the hyperglycemia keeps inhibiting SIRT2, so they keep getting NLRP3-mediated beta cell death, yielding inadequate insulin production, yielding hyperglycemia.

The other problem is that, at the end of the arc of pancreatic beta cell loss is type 2 diabetes (T2D). And in addition to all the other problems with T2D is the fact that insulin is not made by itself. When insulin is made, it's made as pro-insulin, which then divides into insulin and c-peptide. The c-peptide participates in nerve cell repair. If the patient can't make pro-insulin, not only will he be unable to make insulin, he'll also be unable to make c-peptide, which he needs in order to repair nerve cells. At that point, the patient is at risk for failure of peripheral nerve repair (neuropathy) and failure of CNS repair. This is the point I mentioned above, where hyperglycemia / IR can be a driver of dementia. And, if the patient is at risk of other CNS disorders, like MS or PD, the risk can be sharpened by the failure of autophagy.

Likewise, a failure of autophagy of mitochondria (mitophagy) would drive the mitochondrial production of excessive ROS, compounding the concerns described above with regard to mitochondrial over-fueling.

IR, and dysglycemia generally, is one of the most insidiously present and under-treated factors in the typical clinical practice. I find it common to discover that a patient for whom I thought I had handled their glycemic control issue with diet and nutrition, will still have high blood sugar, when they do finger stick and continuous glucose monitoring. In other words, in my mind I've checked the "I handled that issue" box, but I discover later that I didn't sufficiently earn the right to check that box. The patient raises the doses of the things they're taking, or they add a key supplement, or they get more deliberate and complete about their dietary strategy, or they use a CGM to discover a factor they didn't know was spiking their blood sugar, or they use a fasting mimicking diet to reset their metabolism. When they actually get their blood sugar normalized, it can turn the case around.

So, even though blood sugar issues are not mysterious, attending to them in a way that earns you and the patient the right to check the "I handled it" box, can be key.

Assessment

Hemoglobin A1c (HA1c) – This is the percentage of hemoglobin (an easily measured protein) that has a glucose attached (glycated hemoglobin, aka hemoglobin A1c). The higher the percentage glycation, the more often the patient has spent with blood sugar too high in the past 120 days, which is the lifespan of an RBC.

1,5ag (1,5 anhydroglucitol aka Glycomark) – This is a two week window on how often the blood glucose has been too high. Glucose interferes with resorption of 1,5ag in the renal tubule. When glucose levels are high enough for the interference to take place, 1,5ag is lost in the urine, so blood levels go down. A low Glycomark result suggests recent elevation of blood glucose. It's noteworthy that the Glycomark test was created because some patients just never have high HA1c but have high fasting glucose and can become diabetic nonetheless.

C-peptide of insulin – c-peptide is made in equimolar fashion with insulin. Since c-peptide has a longer half-life, its level is considered by some to be a more reliable measure of insulin than blood insulin levels, unless you're in a research setting where the timing of insulin measurement can be better controlled.

SIRT2 inhibitors – uric acid, low potassium, high cholesterol, etc. all need to be considered.

Blood glucose – fasting, post-prandial, etc. It's essential to compare glucose and insulin levels, so you have a sense of whether the patient's insulin production is adequate, well timed, etc. It can be essential to use a CGM. The first thing to do is compare CGM to finger stick (more accurate), which gives you a correction factor for the CGM readings. A CGM may report numbers that are all high, or all low, compared to the finger stick. Once the patient knows the correction factor, it's more reasonable to rely upon the CGM. I have patients use the CGM for two or three days without changing diet, to see what their starting point is, then start to make changes.

Oxidized LDL, Glutathione, TGFβ, F2 isoprostanes, urinary thromboxanes, etc. – to asses ROS. Note that these markers may be more useful in some patients than others.

GlycA and hsCRP (aka cardiac CRP) – inflammatory markers, again sometimes not sensitive.

Other ways of understanding the patient's glycemic status, like symptom surveys, waist/hip ratio, etc., are also useful in the process of assessing insulin resistance. Our chief interest here is the immunology, so I'll leave those discussions for you to find elsewhere.

Treatment

Address Hyperglycemia & Repair Mitochondria

These steps go together. Normalizing the blood sugar takes the stress off mitochondria. Damaged mitochondria need to be removed by mitophagy, so mitophagy needs to be stimulated. And, since IFNɣ promotes autophagy (and therefore mitophagy) and IL-4 inhibits it, T cell polarization needs to be attended to.

1. Modify the diet to reduce caloric intake or change glycemic index, if suitable. Consider the use of intermittent fasting. Consider the use of a fasting mimicking diet, to reset metabolic integrity. This can be done as often as monthly, at the clinician's discretion, for a few cycles, with less frequent cycles once metabolic integrity is improved.
2. Consider **Berberine** to increase uncoupling proteins, diverting some fuel from mitochondria to heat production. This will improve mitochondrial function. Note that patients who complain of being cold but have normal/optimal thyroid lab function may be cold because of low UCP production, or because of T3 resistance, both of which are associated with mitochondrial over-fueling. (for more on this, see Module 21, Videos 12-19).
3. Over-fueled mitochondria generate ROS that drive NFkB, driving insulin resistance. Reducing over-fueling can improving insulin resistance, reduce inflammation, and reduce ROS. If reducing mitochondrial fuel doesn't sufficiently reduce these effects, consider antioxidants like **glutathione** or **alpha lipoic acid** to down-regulate ROS. Consider **Balanced Immune** (Pure Encapsulations) – a source of curcuminoids, resveratrol, black ginger and other substances, to downregulate NFkB.
4. Consider **Renual** (Pure) – 2 BID, a source of urolithin A that promotes mitophagy. Recycling/clearing damaged mitochondria makes way for a healthier population of mitochondria that make less ROS.
5. Consider other substances that play potentially important roles in mitochondrial function, like **coenzyme Q10** and **carnitine.**
6. For some patients, IR is driven by the insulin receptor being shut off too soon, by an intracellular enzyme called PTP1b. Normally, PTP1b shuts off the insulin receptor response to insulin binding after an appropriate amount of time, so each binding hit of insulin to the receptor yields an appropriate amount of cellular response to insulin. But in some people, PTP1b is too efficient, so the insulin receptor is shut off too quickly. This looks like IR. To explore the possibility that over-active PTP1b may be down-regulating insulin receptors, consider using **reishi** aka **ganoderma**, 1 or 2 grams at bedtime. See if you find a dose that lowers morning glucose enough to make a real difference. If ganoderma does lower morning glucose, it suggests that the inhibitory effect of ganoderma on PTP1b has been useful, implying that this patient has over-active PTP1b. If that's the case, the patient should take ganoderma with each meal. Figure out how far before the meal the patient needs to take it, and how much they need to take, to improve insulin receptor response. If fasting glucose is unchanged by ganoderma, this approach isn't relevant to the case.
7. Consider substances that play a role in normal glycemic control, like chromium, vanadium, bitter melon, and other glycemic control substances. **Glucofunction** (Pure Encapsulations) is a good choice to consider.

Inflammasome Activation / Inflammation Driving Insulin Resistance

1. **Balanced Immune** (Pure) – 2 or 3 BID, to downregulate NFkB. Note that NFkB activation is an essential step in inflammasome activation.
2. **Vitamin D** – dose to get blood level in the top quintile of the normal range, without going out the top of the range. This is especially important when there's a concern about VDR downregulation due to the presence of EBV.
3. **Uric Acid Formula** (Pure) – 2 BID, to downregulate uric acid.
4. **Morus Alba** – this can be especially useful in downregulating uric acid.
5. Address hyperglycemia.

Address T cell polarization

1. **Th1 Support** (Pure) – 2 BID, to support adequate Th1/NK cell response to down-regulate EBV burden, so VDR's can work properly. Note that this contains berberine, which will help with mitochondrial over-fueling.
2. **Th2 Modulator** (Pure) – 2 BID, to downregulate over-active Th2 response.
3. **Perilla Extract** (Pure) – 2 BID, to give a stronger downregulation to IL-4, in patients with more entrenched Th2 dominance.
4. As always, when attending to T cell polarization issues, it's necessary to identify factors in the case that promote problematic shifts in T cell polarization. These could include stress chemistry, dysbiosis, sleep disruption, overtraining, fungal or other infection, etc.

The Importance of Context

In the overall picture of glycemic control, keep in mind that there are problems at both the high and low end of glycemic function. When you ask the patient to control blood sugar, there can also be a risk at the low end of the glucose range. If the patient goes on a very low carb diet, that could work for a while to improve mitochondrial function and metabolic integrity and to reduce inflammation. But if the glucose level is kept very low, the body will make much less insulin. If insulin production goes down, the c-peptide level will also be lower since insulin and c-peptide both come from pro-insulin, which splits to form one molecule of insulin and one of c-peptide. c-peptide is essential for nerve cell repair. If a very-low-carb/very low blood sugar diet is maintained across too much time (months instead of weeks), the patient risks developing a neuropathy or problems related to poor CNS repair.