Origins of Insulin Resistance and Metabolic Syndrome

From the Show Notes of a podcast interview of Gerald Shulman, MD by Peter Attia, MD

Synopsis of the Synopsis

- Gerald says that insulin resistance is quite common—**he estimates one quarter to one half of the population is affected by it without notable symptoms.**
- **In a healthy individual, 80-90% of consumed glucose is stored as glycogen (in muscle and liver)**.
- In type 2 diabetics, there are two processes that have "gone awry," leading to the elevated blood glucose. The first is that **the liver produces more glucose through gluconeogenesis**, which involves conversion of metabolites like amino acids and lactate into glucose. The second is that **less glucose is being taken up by muscle**.
- Gerald estimates up to half the people in the U.S. have insulin resistance but are asymptomatic. **He has seen young, lean 20-year-olds that have *profound insulin resistance in the muscle*, yet no problems in the liver.**
- **The progression goes from insulin resistance in muscle, to fatty liver and insulin resistance in the liver, and then to type 2 diabetes.**
- **Insulin signals the muscle, liver, and fat to take up glucose. Insulin also signals the liver to stop making glucose and the fat cells to slow or stop lipolysis, as well as to take up fatty acids for esterification.** So, an impaired ability to do any of those things in the presence of insulin is what we call insulin resistance.
- The block causing insulin resistance in muscle is in the process of transport of glucose.
- **Gerald developed a method to measure fat inside the muscle cell. He found that this fat was the best predictor for insulin resistance in muscle and a block in translocation of the GLUT4 transporter, with subsequent lack of glucose uptake.**
- **A triglyceride is a glycerol backbone with three fatty acids attached. A diacylglycerol is a glycerol backbone with one fatty acid removed.**
- **When the flow of fatty acids into the muscle cell exceeds the ability of mitochondria to oxidize the fat, or store the fat as triglycerides, you get a net accumulation of diacylglycerol along with triglycerides. Triglycerides are neutral. Diacylglycerols track with and likely cause insulin resistance.**
- **Gerald says exercise reverses muscle insulin resistance as well as prevents fatty liver and liver insulin resistance.**
- I**nsulin resistance in muscle leads to *de novo* lipogenesis and fat accumulation *in the liver,* leading to increased very-low density lipoprotein (VLDL) production by the liver, increased blood triglyceride levels, and decreased high-density lipoprotein (HDL) levels.**

- **These IR people in their basal state take up less than half the amount of glucose in muscle due to a block in transport (as discussed previously). (This carbohydrate then must be disposed of in some other way. It is taken up by the liver and converted into fat.**)
- **De novo lipogenesis becomes more important in the context of insulin resistance and can contribute to development of fatty liver disease.**
- Meal content can influence de novo lipogenesis as well. **Fructose in particular fuels this pathway.**
- ***All this de novo lipogenesis can happen while a person is still has normal blood sugar.*** According to Peter Attia, these people may be a decade away from having an elevated blood sugar.
- **Just one 45-min bout of aerobic exercise (three 15-minute sets at 65% of maximal aerobic capacity, each separated by 5 minutes of rest) restored the concentration of glucose 6-phosphate and the rate of glycogen synthesis in the muscle of insulin-resistant participants to that of the baseline (pre-exercise) level of the insulin-sensitive participants**.
- In the healthy, young, and lean individuals Gerald has worked with, they have insulin resistance in muscle, but their livers are healthy. Insulin resistance in muscle diverts glucose to the liver, leading to fat accumulation there**. At this point, insulin resistance is present in both the liver and muscle.**
- **In contrast to muscle, insulin is not required to stimulate glucose uptake in the liver. Instead of GLUT4, the primary transporter for glucose in the liver is glucose transporter 2 (GLUT2), which translocates to the cell membrane independently of insulin.**
- **(It appears that the insulin resistance in the muscle leads to the need for disposal of the excess glucose in the liver. The system is overwhelmed leading to generation of more fat which then accumulates in the liver. This fat accumulation leads to insulin resistance because of the increase in diacylglycerol. The insulin resistance in the liver then leads to the increased gluconeogenesis and the decrease in glycogen synthesis, ending in diabetes.)**
- **"In my view, insulin resistance was a protective mechanism throughout evolution that allowed us to survive…starvation which was probably the predominant environmental exposure we've had for the last many, many millennia. It's only in recent years, recent decades and now we're in this toxic environment of over-nutrition and it's when these same pathways now are going the opposite direction— promoting disease by doing what they were at one time was protective. And now they're actually being called metabolic disease."**
- **In a healthy state, when you eat, your insulin will go up. One of the tissues that is affected by insulin are fat cells. In fat cells, insulin prevents the breakdown of triglycerides into free fatty acids. It is the presence of free fatty acids that provide the signal for the body to make sugar from protein and other sources.**
- **If there is insulin resistance in the fat cells, especially if accompanied by inflammation, then there is no inhibition of the breakdown of triglycerides,**

and no brake on production of glucose, even though you have plenty of glucose on board.

- **The transition from insulin resistance in muscle and in liver to fasting hyperglycemia *requires* inflammation**. In the context of obesity and diabetes, ***you have localized inflammation in the fat cells. The presence of inflammatory cytokines results in increased lipolysis, leading to greater delivery of fatty acids to the liver, more accumulation of diacylglycerol*** and, in turn, more hepatic insulin resistance and less storage of glucose as liver glycogen. This is what happens to most patients with fatty liver disease.
- **What takes you to fasting hyperglycemia is this**: **acetyl-CoA goes up, lipolysis and fatty acid turnover goes up two-fold. This increases acetyl-CoA concentrations two-fold. This activates pyruvate carboxylase activity and flux two-fold. (This increases gluconeogenesis). In addition, your glycerol delivery is up two-fold. This drives an increase in gluconeogenesis two-fold. This is what drives hyperglycemia in most poorly controlled type 2 diabetics.**
- **In general, Gerald believes that it is diacylglycerol that initially drives insulin resistance and subsequent increases in acetyl-CoA and gluconeogenesis that facilitate transition to fasting hyperglycemia and diabetes.**