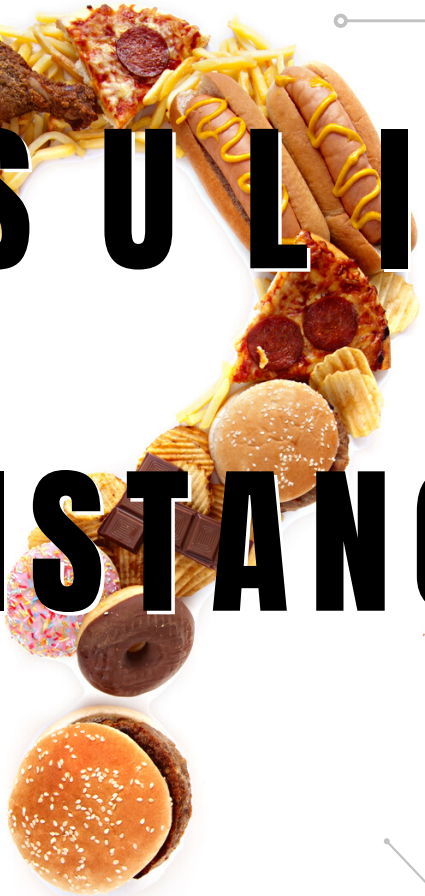
THE ALARMING EPIDEMIC THAT IS DESTROYING WORLD HEALTH

INSULIN RESISTANCE



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We are sick. Worldwide we are dying from diseases that were once unheard of. Each year, roughly 10 million people die from cancer and almost 20 million people die from heart disease. Up to half a billion people have diabetes. Less lethal, though highly relevant, 40% of men over 45 suffer from complications of low testosterone and almost 10% of women experience menstrual irregularities and infertility. All of these disorders and more have one thing in common—each of them, to varying degrees, is caused or exacerbated by a change in the levels and actions of the hormone insulin, a condition known as insulin resistance. And you might have it. Odds are you do—half of all adults in the USA, Mexico, China, and India do, with more than a third of adults in Europe and Canada; the problem is even worse across the Pacific Islands, North Africa, and the Middle East. Thus, it's no surprise that insulin resistance is the most common health disorder among adults worldwide.

Do you think you or a loved one might be insulin resistant? Answer the questions below:

- Do you have more fat around your belly than you'd like?
- Do you have high blood pressure or a family history of heart disease?
- Do you have high blood pressure or does eating salt affect your blood pressure?
- Do you have high levels of blood triglycerides?
- Do you retain water easily?
- Do you have gout?
- Do you have patches of darker colored skin or little bumps of skin ("skin tags") at your neck, armpits, or other areas?
- Do you have a family member with insulin resistance or type 2 diabetes?
- Do you have/had gestational diabetes or PCOS (for women) or have "low testosterone (for men)?

If you answered 'yes' to any two questions (or more), this book is for you. Read it and learn about the most common non-infectious disorder in the world; why it's so common, why you should care, and what you can do about it.

THE PROBLEM

Insulin resistance is defined as a reduced response to the hormone insulin. Every cell in every tissue of the body responds to insulin. Insulin, which is flowing in the blood, will bind to a specific site on a cell and then elicit a series of events within that cell. The event depends on the cell. For example, when insulin binds to a liver cell, the liver cell makes fat (among other things); when insulin binds to a fat cell, the cell makes new fats (among other things). Common among all of its effects is insulin's ability to have the cell make bigger things out of smaller things, a process known as anabolism. When a cell loses its responsiveness to insulin, which can happen as a consequence of various conditions (covered later), it becomes insulin resistant. Ultimately, as more cells throughout the body become insulin resistant, the body, then, is considered insulin resistant. In such a state, the cells need more than normal amounts of insulin in order to get the same response as before. Thus, the key feature of insulin resistance is that: 1) blood levels of insulin are higher than they used to be and, in many instances; 2)the insulin doesn't work as well.

But what about glucose? Insulin certainly affects glucose, and vice versa. When we eat a starchy or sugary meal, blood glucose rises. Because sustained high glucose levels ("hyperglycemia") is potentially lethal, insulin spikes and, among its other effects, opens the doors on various cells (like muscle and fat) and ushers the glucose from the blood, effectively lowering blood glucose back to normal.

Naturally, as insulin resistance settles in, this process becomes compromised, which can lead to hyperglycemia, the universal sign of diabetes. But we're getting ahead of ourselves.

A Metabolic Pandemic

Insulin resistance is the epidemic you have never heard of; over half of all adults and roughly 1 in 3 Americans have the disorder [1, 2]. Even more disturbing than how common the disorder is currently is how common it's going to be—up to 10% of children are insulin resistant [3], compared to none just years ago. But don't think the problem is a local one. When we look at worldwide trends, it gets even grimmer—80% of all individuals with insulin resistance live in developing countries, and, similar to the US, half of all adults in China and India are insulin resistant. Even still, this isn't a new trend—the number of cases of insulin resistance worldwide has doubled in the past three decades and will likely double again in less than two decades. This was once a plague of prosperity that largely affected only older people, but that has changed dramatically—there are documented reports of four-year-olds with insulin resistance.

To top it all off, the overwhelming majority of people with insulin resistance don't know they have it! This means people are experiencing multiple and seemingly diverse health problems that could be improved by addressing one common problem—insulin resistance. Indeed, insulin resistance is a disorder that has a hand in a startling number of chronic and even very serious diseases—ranging from problems of the head, heart, blood vessels, reproductive organs, and more.

Insulin is almost always considered in the context of glucose, which isn't entirely fair considering the hundreds (thousands?) of things insulin does throughout the body. Nevertheless, in a healthy body, if blood glucose is normal, insulin is usually normal. However, with insulin resistance, insulin levels are higher than expected relative to glucose.

The glucose-centric paradigm of insulin resistance and type 2 diabetes can likely be blamed on history and science. Historically, due to its causal role with type 2 diabetes, insulin resistance has been lumped into the diabetes mellitus family of diseases. The first recorded evidence of this family of diseases is ancient Egypt, where it was noted that people with a particular disease experienced "too great emptying of the urine." Around this same time, Indian physicians were noting individuals who produced urine that attracted insects like honey ("mellitus" means sweet). Hundreds of years later, in Greece, the excessive urine associated with the disease elicited the name "diabete", which means "to pass through", further emphasizing the remarkable amount of urine patients were producing. Have you noticed the common finding? In each case, the excessive urine production was accompanied with weight loss. In fact, though it seems amusing now, early theories were that the flesh was melting into urine. Of course, these early physicians, and those that came later, were describing type 1 diabetes mellitus. It wasn't until the fifth century that Indian physicians noted two distinct types of diabetes mellitus—one associated with a young age and losing weight, the other with older age and excess body weight. Nonetheless, both were identified by the excess amount of glucose-loaded urine, which, in the absence of savvier techniques, understandably lead to the disease being defined by glucose; the glucose was causing the common main observable symptom (i.e. polyuria).

However, in doing so, we ignored the other and more relevant half of the problem—insulin. And while type 1 and type 2 diabetes share a similar symptom with excess glucose, they diverge completely when it comes to insulin. Whereas type 1 diabetes is caused by having too little insulin (or none), type 2 is caused by having too much. This 'too much insulin' is insulin resistance, and because of its association with type 2 diabetes, it became wrapped up in the glucose-centric perspective as well.

Scientifically, glucose is more easily measured than insulin. To measure glucose, we only need a simple enzyme on a stick (e.g., glucometer), which we've been able to do for roughly 100 years. Insulin, on the other hand, by nature of its molecular structure and characteristics, is much more difficult to measure and, thus, the procedure is much more recent. It wasn't until the late 1950s that we could measure insulin, and even still, it required handling radioactive material to do so.

So, even though we could now measure insulin (and it's even simpler now), it was too late—we'd already committed to thinking of the diabetes as being a "glucose disease", and, in turn, developed clinical diagnostic values for the disease based entirely on glucose. Indeed, if you were to take a quick moment and conduct an Internet search for "glucose+diabetes" several top results would immediately inform you of the clinical values of blood glucose for diabetes—type 1 and type 2. But try a similar search for insulin, and you'll find nothing; even for a professional scientist who studies insulin and insulin resistance, I have a hard time finding a consensus on insulin values for diabetes.

Really, excess glucose is the only thing type 1 and type 2 diabetes have in common—other than glucose, they are wildly different diseases with very different symptoms and progressions.

The best method is unfortunately one that is difficult to do—a frequently sampled blood insulin test following a glucose challenge. In short, after drinking a load of glucose, you get your blood drawn to measure insulin roughly every 30 minutes for 2-3 hours [4].

All of this is interesting, but it still doesn't really hit the important point of why so many people with insulin resistance are undiagnosed. After all, if we can identify type 2 diabetes by glucose, why not insulin resistance (which is also called "prediabetes")? We fail to identify it because insulin resistance isn't necessarily a hyperglycemic state. In other words, someone can have insulin resistance and enjoy perfectly normal blood glucose levels. But which value won't be normal in insulin resistance? You guessed it—insulin; if you're insulin resistant, you'll have higher than normal levels of insulin. But of course a problem is both finding a consensus value for blood insulin, as well as actually getting your blood insulin measured clinically. Thus, we can have a scenario where a person is steadily becoming more and more insulin resistant, but the insulin is sufficient to keep blood glucose in a normal range. This can occur over years, even decades. But because we more typically look at glucose as the problem, it isn't until the person is so insulin resistant that his insulin, no matter how much he produces, is no longer enough to keep blood glucose in check. And it's at this point, possibly years after the problem started, that we finally notice the disease—only once glucose is increased.

Before moving on, it's helpful to establish a couple points up front. First, as mentioned, insulin resistance increases the risk of type 2 diabetes. This is true, but this relationship warrants additional clarification. Type 2 diabetes is insulin resistance; type 2 diabetes is insulin resistance that has progressed to the point where the body is unable to keep blood glucose levels below the clinically relevant set point of 126 mg/dl. That type 2 diabetes mellitus is simply insulin resistance that has gone too far has been known for almost 100 years, first proposed in 1931 by the German scientist Wilhelm Falta [5, 6]. Second, insulin resistance is a hyperinsulinemic state—that means a person with insulin resistance has more insulin in the blood than normal. This particular point becomes highly relevant as we discuss the unfortunate effects of having too much insulin in the blood for prolonged periods of time.

As a reminder, it is noteworthy that insulin resistance per se won't kill you—no one dies from insulin resistance—it's simply a vehicle that gets you there. After developing type 2 diabetes, most people will ultimately die from heart disease or other cardiovascular complications; others will suffer from Alzheimer disease, or any other number of chronic diseases, which we'll cover after looking at what causes insulin resistance.

CAUSES

Considering the remarkable rise in the prevalence of insulin resistance, substantial attention has been devoted to trying to understand how insulin resistance develops. Some of these discoveries have been novel (i.e., genetics), while others have been more of a rediscovery of lessons from the past (i.e., lifestyle); all are worth mentioning.

Insulin

Too much insulin causes insulin resistance. Of the various factors that can cause insulin resistance (and we'll discuss them all), insulin is the most relevant. To be precise about it, for every 1 μU change in blood insulin level (a pretty small change), a person can experience an approximately 20% increase in insulin resistance [7]. This might seem like a strange cause and effect, but it represents a fundamental feature of how the body works: when a process is excessively activated, the body will often dampen its response to the excess stimulus in order to reduce the activation. This is similar to how bacteria become resistant to antibiotics or how a caffeine addict needs more caffeine than she used to. With insulin resistance, if a cell, such as those of the muscle or liver, is inundated with insulin, it can do nothing to directly reduce the insulin being produced, which is happening at the pancreas, but it can alter itself to ensure that insulin has a smaller effect; thus, it becomes resistant to insulin. As this occurs in countless cells in several tissues throughout the body, the body as a whole becomes insulin resistant.

The studies that have highlighted this phenomenon of elevated blood insulin (i.e. hyperinsulinemia) causing insulin resistance are convincing and distinct from one another. For example, certain pancreas tumors consist of overactive beta cells, the cells that create and release insulin; this is a tumor known as an insulinoma. Thus, these patients have elevated blood insulin, which is entirely a result of the tumor. The patients with the highest degree of insulin production from the insulinoma become highly insulin resistant, whereas the patients with the lower insulin levels become mildly insulin resistant. But, in the end, they always develop insulin resistance [8, 9].

In another instance, scientists caused an artificial hyperinsulinemia (i.e., high blood insulin) by infusing healthy insulin-sensitive men with insulin for a prolonged period [10]. Even though the insulin dose was at a physiologic level (i.e., a level normally reached in the day), by keeping a steady infusion, the men become insulin resistant after just a few hours. While this scenario is somewhat unrealistic (after all, nobody normally sits in a chair while receiving an insulin infusion), it nonetheless reflects a condition that would exist if a person were snacking often on insulin-spiking foods (i.e. most people).

Obesity

Obesity—the elephant in the room. There is no doubt that excess body fat is related to insulin resistance. Most overweight/obese individuals are insulin resistant (~70%) and because insulin resistance is so commonly associated with excess body fat, plenty of scientists have tried to find out why.

That obesity and insulin resistance tend to occur together has been observed for roughly a century, as scientists on both sides of the ocean were learning more about insulin, but we only started looking at obesity and insulin resistance in a causal relationship within the last three decades or so. The result of much of this focus has been to conclude that obesity drives insulin resistance. Indeed, this is the predominant paradigm and, as evidence, the term "obesity-induced insulin resistance" is a common part of the vernacular in this area of research and an internet search yields thousands of hits on biomedical research search engines. But it's not that simple.

Location Matters

As with real estate, so it is with body fat—it's all about location. Increasingly, we appreciate that excess body fat is largely relevant only if we store our fat in the wrong place. Where we store our fat is determined largely by our sex, partly by our genetics ("thanks Mom and Dad"), and partly by diet.

Typically, we consider two predominant 'patterns' of fat storage, referred to as fat deposition, although there are always exceptions and some may have the misfortune of having both.

First, the "gynecoid" fat pattern is analogous to a person with a pear-shape body, typically seen with females due to the actions of estrogen hormones (the predominant 'female' hormones). This pattern is typified by fat accumulating on the hips and thighs, with less fat on the upper body and trunk.

Second, the "android" deposition is the typical male fat storage and is considered analogous to someone having a body shaped like an apple. This is the person who stores most body fat right around the middle of the body—the 'inner tube'.

We have long known that women have a better chance of living a longer, healthier life than men; this is partly due to the inherent differences in the impact these fat depots have on insulin resistance and the subsequent risk of various chronic diseases. Ultimately, what is so important about these two fat patterns is the likelihood of having excess fat in the "visceral" space—inside the trunk of the body, surrounding the visceral organs (e.g., liver, kidneys, intestines, heart, etc.). Study after study has shown that storing fat inside the core of the body is harmful and we now know that there are differences in how fat behaves when it's stored in the viscera. Naturally, people who tend to store more fat in the center of the body have a greater likelihood of storing more fat in the viscera, which is why men typically have more visceral fat than women. And this, in turn, is likely why men suffer more health problems with excess body fat than women.

Interestingly, these same rules apply to a seemingly lean person. That's right—even some people who are 'lean' may be insulin resistant because of having more visceral fat. But wait: even 'lean' individuals with insulin resistance are likely fatter than their 'lean' insulin-sensitive counterparts. It's really a matter of whether you see the fat or not. And this is relevant because it emphasizes the most important aspect of obesity and insulin resistance; namely, where you're fat.

Ultimately, the story still isn't over; it isn't enough to know that excess body fat increases the risk of developing insulin resistance. We need to know how the fat leads to insulin resistance. Excess body fat, especially visceral fat more so than subcutaneous fat, increases two pathological conditions—it increases inflammation and causes oxidative stress (covered in the next two chapters).

Size Matters

Did you know that your fat cells may be able to only hold so much fat? Like an overflowing cup, when your fat cells are "full", the excess fat begins spilling over into the blood, increasing blood free fatty acids and potentially getting stored in non-fat tissues. The problem with this, of course, is that other tissues aren't designed for long-term fat storage—that's the job of the fat tissue, after all. This is known as ectopic fat accrual or lipotoxicity.

A remarkable aspect of this process is that as the excess fat is accumulating in other tissues, like the liver and muscles, the fat turns into various, even nefarious, kinds of fat molecules. Rather than the simple "storage mode" fat we know as triglycerides, which is benign with regards to insulin signaling [11], this ectopic lipid can readily become more "toxic" fats that antagonize the process of insulin acting on a cell.

The precise process whereby fat cells become unable to store more fat is being actively studied, but one of the most likely explanations is also one of the simplest; it's all about size. Larger fat cells have relatively fewer insulin receptors, for their size, than smaller fat cells [12]. Because of this, larger fat cells may not receive sufficient insulin stimulus and as a result, the larger fat cells are continually "leaking" fat. Regardless of the mechanism, we know clearly that having more, yet smaller fat cells is better, metabolically speaking, than having fewer, but larger fat cells [13].

Inflammation

In thinking about inflammation, you're very likely imagining a red, swollen, painful injury, but that's not the inflammation we're talking about in the context of insulin resistance. In this case, inflammation refers to an increase in the production of proteins from immune cells, such as macrophages and neutrophils, that turn on immune-related responses throughout the body that can be so subtle they're almost undetectable.

The earliest research identifying the role of inflammation as a cause of insulin resistance came from studying the problems that accompany infections—people with prolonged infections (which naturally comes along with an increase in immunity-inflammation processes) have insulin resistance [14]. This is most obviously relevant in a person who is experiencing an infection-related illness, such as infectious mononucleosis [15]. Periodontitis, which is inflammation of the gums of the mouth, can also cause insulin resistance [16-18]. However, inflammation and insulin resistance is also relevant in autoimmune diseases, where the body is attacking itself by using the immune pathways activated by those proteins mentioned above. For example, the inflammatory joint disease rheumatoid arthritis, where a person's body is destroying their own joints, is heavily associated with insulin resistance to the point that those individuals who experience the worst inflammation also experience the greatest insulin resistance [19-21]. The same effect is seen with other inflammatory autoimmune diseases, such as lupus [21] and crohn's disease [22]. Even the most toxic and lethal forms of inflammation, such as sepsis, leads to insulin resistance [23].

Far less serious than sepsis, though far more common, obesity is also an inflammatory disorder. As a person gains fat, the level of immune proteins in the blood increases to the point that, in many instances, obesity is referred to as a state of chronic inflammation [24]. While inflammation is less obvious with obesity, and certainly less noticeable, than overt inflammatory diseases like rheumatoid arthritis, its effects are nonetheless felt, even with insulin resistance. In the early 1990s, reports were published that detailed how fat tissue itself contributes to inflammation and ultimately causes insulin resistance [25].

What appears to be so important in connecting obesity and insulin resistance is what the excess body fat does to the immune system in two opposing states of nutrition. With 'undernutrition', where a person is not receiving sufficient nutrition, the immune system is compromised—it is weaker and the person experiences more infections and illness [26]. In stark contrast, when a person is 'overnourished', a state where a person is increasing their body fat because of their diet, the immune system appears to be ramped up, almost as if it's fighting an infection that isn't there. Altogether, this series of events increases whole-body inflammation to a level that is higher than normal, yet not to the level of clinical significance, referred to as "subclinical chronic inflammation".

As stated above, visceral fat is more harmful than subcutaneous fat. Understandably, too much fat storage surrounding our internal organs could become problematic—the fat could start to impede the function of the organs. Possibly in an effort to remove the fat from these fat cells and reduce the size of the fat, visceral fat tissue becomes populated with macrophages, the prototypical white blood cell whose main job is to clean up cellular messes. Unfortunately, as an individual continues to accrue visceral fat (due to diet?), the macrophage begins to lose the battle and becomes itself filled with fat—this sort of lipid-loaded macrophage is known as a 'foam cell' due to its foamy (with fat) appearance under a microscope. This foam cell macrophage begins to recruit help—it calls out to other macrophages by sending out inflammatory proteins that inform other macrophages to come to the area. The newcomers also become foam cells over time, feeding the problem forward.

Once inflammatory pathways are activated, regardless of the cause, the cellular changes that then lead to insulin resistance are poorly understood, though some evidence exists. In particular, regardless of the cause, inflammation increases the accumulation of a fat molecule called ceramide [27, 28], and where ceramide accumulates, a tissue becomes insulin resistant [29].

Stress

Stress is an ambiguous term that is used to apply to a host of stimuli that harm the body; these can range from physical (e.g., starvation, infection, etc.) to mental (e.g., concern for a loved one, anxiety for an event, etc.). Remarkably, despite these very different scenarios, the same processes in the body are activated—this is the "stress response."

Cortisol

The stress response involves an interesting mix of neural and endocrine (hormone) events that ultimately result in the increased release of a hormone called cortisol, which is released from the adrenal glands. While other hormones are released into the blood with stress, cortisol is considered the prototypical stress hormone, and many of the consequences of stress are a result of cortisol's actions on the body. Paramount among its various actions is cortisol's determination to raise blood glucose—cortisol will tell the liver to make glucose out of anything it can get its hands on, including amino acids (from protein) and glycerol (from fats), in order to ensure that the body has enough glucose to fuel metabolic processes to get through what you perceive to be a stressful situation (i.e., running away from a predator, stay up late studying, etc.).

While cortisol is trying to increase blood glucose, insulin is trying to reduce blood glucose—these two are counter-regulatory—they act against one another. But in this fight, cortisol wins; cortisol makes the body remarkably insulin resistant, which as associated with a steady increase in blood insulin over time. One of the more dramatic situations that perfectly typify this scenario is Cushing Syndrome—a family of disorders that results from the adrenal glands producing too much cortisol. As you would expect, individuals who develop Cushing Syndrome as a result of a hormone or other abnormality go from being perfectly insulin sensitive to highly insulin resistant after the cortisol starts to climb.

Epinephrine

Cortisol is the clear champion of stress—most of the effects on the body during stress result from too much cortisol for too long, including insulin resistance. However, in the earliest stages of stress, a different hormone is more relevant. Epinephrine, the early stress hormone, is released from the adrenal glands, like cortisol. Most of epinephrine's effects are obvious in changes in hemodynamics—epinephrine increases heart rate and blood pressure. But too much epinephrine for too long, like cortisol, is also capable of causing insulin resistance [30].

Up to this point, we've discussed the myriad ways whereby the world around and how we interact with it can cause our bodies to become insulin resistant. Much of it is centered on what we put in our bodies and how this affects insulin, which then affects the degree to which the body's cells are responsive to insulin. With this behind us, we're prepared to dive into why insulin resistance really matters. The consequences of insulin resistance, ranging from inconvenient to lethal, arise as either a consequence of the cells failing to respond to insulin (i.e., insulin resistance) or there being too much insulin in the blood (i.e., hyperinsulinemia). Take a big breath—it's a deep dive.

Cardiovascular Disorders

The most common cause of death among people with insulin resistance is heart disease. This isn't entirely surprising when we appreciate that heart disease is the number one killer in most developed countries [31] and insulin resistance, of course, is the most common disorder. Heart disease is an umbrella term for several disorders that affect our cardiovascular system, including blood vessel disorders, coronary artery disease, arrhythmias, atherosclerosis, and more. Due to the number of people dying from heart disease, a great deal of research attention has focused on the factors that cause heart disease or make it progress more rapidly. A result of these efforts has been identifying the very robust relationship between heart disease and insulin resistance [32-36]. Indeed, the connection between insulin resistance and heart disease is so remarkably strong that entire biomedical journals are dedicated to publishing dozens of science articles every month on the topic.

But it's more than coincidence that insulin resistance is the most common disorder and heart disease the most common killer—the two are almost inseparable. A preeminent physician-scientist, Dr. Joseph Kraft, who devoted his remarkably prolific career to understanding insulin resistance, accurately declared in his book The Diabetes Epidemic and You, "Those with cardiovascular disease not identified with diabetes [i.e. insulin resistance] are simply undiagnosed." Where you find one, you find the other.

Hypertension

Having excessively high blood pressure dramatically increases the likelihood of developing heart disease and is a leading risk factor for the disease. As the pressure in your blood vessels increases, your heart has to continually work harder to ensure that the blood is adequately moving throughout the body and all its tissues (e.g., liver, muscles, brain, etc.). Naturally, this strain on the heart can only be met for so long, ultimately resulting in the heart failing.

That insulin resistance is related to hypertension is not debated—the consistency of a patient having both is evidence of a clear association and almost all people with hypertension are insulin resistant [37]. However, over the years, we've come to understand very clear consequences; that insulin resistance and the accompanying hyperinsulinemia increase blood pressure through several distinct mechanisms working in concert to chronically increase blood pressure, outlined below [38]. The reason this is so important, as you'll recall, is that the overwhelming majority of people with insulin resistance don't know they have it. Thus, in a way, hypertension may be the first evidence of insulin resistance.

Excess Aldosterone Production

A primary mechanism whereby insulin increases blood pressure is through its actions on the hormone aldosterone. Aldosterone is released from the adrenal glands (above the kidneys) and acts to increase the amount of sodium the kidneys reabsorb into the blood (rather than stay in the urine and be passed from the body). Thus, if adrenal glands release more aldosterone into the blood, it will act to increase the amount of sodium the body retains, and where sodium goes, so too does water. This retained water will lead to an increase in the amount of water in the blood, effectively increasing the blood volume. As the volume of the blood increases, the pressure steadily climbs. Because insulin has a natural effect to increase aldosterone levels in the body, if you have more insulin (e.g., hyperinsulinemia), such as what accompanies insulin resistance, this process of insulin leading to increased aldosterone is happening to a greater degree than normal, increasing blood volume and potentially raising blood pressure. This is very likely a mechanism to explain the remarkably tight association of insulin resistance and increased blood pressure. It also explains why carbohydrates, which increase insulin more than other nutrients, so effectively increase blood pressure [39, 40], while dietary fat does nothing [41].

Enhanced Blood Vessel Wall Growth

Blood vessels are lined with cells known as “endothelial cells” or the “endothelium.” Insulin is an anabolic hormone—it inherently tells cells to get bigger. This is a healthy and natural response. However, when excess insulin is flowing through the blood, the signal to tell endothelial cells to grow is stronger than normal. The result is that as the endothelial cells that line the blood vessel start to thicken, blood vessels begin to narrow. This is like having the walls of a garden hose start to thicken as water is flowing through it; you can imagine that as the sides of the hose start to press in on the flowing water, the pressure inside the hose starts to climb. This is exactly what happens in the blood vessels as too much insulin excessively stimulates the growth of the endothelium.

Sympathetic Nervous System

The sympathetic nervous system (SNS) is a function within our body that regulates the body's unconscious actions, including heart rate and heart contraction force, blood vessel size, sweat glands and more. The SNS is typically referred to as the "fight or flight response", given that its events tend to drive the body to action—it primes the pump for us to physically perform at our best. A part of this overall action is to increase blood pressure, which, when you're fighting for your survival, is very helpful, insofar as it can increase the delivery of blood (with all its nutrients and oxygen) to various tissues throughout the body. Interestingly, insulin turns this process on, albeit subtly. However, once again, when you have too much insulin with insulin resistance, this process is hyperactive—we're slightly activating the fight or flight response to such a degree that we experience an increase in blood pressure, which will last as long as the insulin is elevated.

Nitric Oxide

Nitric oxide (NO) is a powerful "vasodilator", which means it increases the diameter of a blood vessel. Just as you'd expected, as a blood vessel increases in diameter, the pressure in the vessel plummets. This effect is so rapid and potent that we have long used NO (e.g., in the form of oral nitroglycerine) to rapidly increase blood flow to tissues and protect them from ischemia (i.e., too little blood), such as in the event of chest pain. In fact, NO has been shown to be so important in cardiovascular health that scientists exploring its function received the Nobel prize.

Insulin has an agonistic effect on NO production in endothelial cells—when insulin flows through a series of blood vessels, one of its actions will be to increase vessel diameter via NO to increase blood blow to the area [42]. This may be one of the ways insulin directs the flow and use of nutrients by various tissues. In contrast to the previous mechanisms, where aldosterone, endothelial growth, and SNS are all overactive with insulin resistance (because of the hyperinsulinemia), the problem with NO and insulin resistance is that NO is less active. In this scenario, the endothelial cells have become less responsive to insulin's actions to increase NO production. Thus, where insulin once increased blood vessel size and reduced blood pressure, it now has no effect.

Dyslipidemia

Dyslipidemia is simply a state of having an abnormal amount of lipids (fats) in your blood. Usually, this is defined by simply having too much lipid (e.g., hyperlipidemia), but it can also indicate that the usual levels of the various lipids are simply out of order. The main lipid players are the usual suspects: triglycerides (TG), low-density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterol.

The clear cultural (dogmatic) consensus is that LDL cholesterol is the villain among the lipid list of suspects, and while there are certainly data to support that conclusion [43], there are many, many studies that suggest otherwise [44, 45]. The controversy surrounding the lack of consistent evidence to support the theory that LDL is as lethal as we once believed may have to do with how we measure it.

LDL cholesterol comes in various sizes and density, and measuring this is getting easier and easier to do. We now know (and have for a while) that LDL is more relevant when it is categorized by size and density, which we refer to as a "pattern". There are two patterns, A and B, that each represent the ends of a spectrum where A refers to an LDL molecule that is large is less dense, and B refers to the LDL being smaller and denser. When we consider that for the cholesterol carrier to be pathogenic it must pass from the blood and into the blood vessel wall, we can appreciate that the smaller, denser lipoprotein would do this more easily. If this doesn't make sense, let's use an analogy. Imagine you are standing on a bridge above a river. In your left hand, you're holding a beach ball (i.e. LDL A; more buoyant, less dense); in your right hand, you're holding a golf ball (i.e. LDL B; less buoyant, denser). As you drop both balls, what would happen? The beach ball (i.e. LDL B) would float along with the river, while, as any golfer knows, the golf ball (i.e., LDL B) would drop to the bottom, bouncing along the riverbed. LDL A and B act in a similar way; LDL A tends to interact with the blood vessel wall less frequently than LDL B. And LDL can only drop off its fats and cholesterol when it bumps into the blood vessel well. Thus, it's not surprising that people with LDL pattern B are remarkably more likely to experience cardiovascular complications than people with pattern A [46].

However, at this point, determining LDL size is still not a common part of typical blood tests, which usually just includes the main three players with regards to lipids: TG, LDL, and HDL. Interestingly, however, we can use two of those numbers as a highly accurate indicator of LDL size—a "poor man's" method. By dividing TG by HDL (TG/HDL), we get a ratio that is surprisingly accurate in predicting LDL size. The lower the ratio (e.g., ~<1.5), the more prevalent the larger, buoyant LDL particles, (i.e., LDL pattern A predominates). But as the ratio climbs (~>2), the small, dense LDL particles become more common (i.e., pattern B predominates) [47]. Again, the benefit of this ratio is that virtually every blood test will include these two variables (i.e., TG and HDL), which means we can readily get an idea of our individual LDL pattern type.

But what does all this have to do with insulin resistance? Insulin selectively drives the production of LDL pattern B from the liver (where almost all cholesterol is made), and as insulin levels steadily climb with increasing insulin resistance, the liver is getting the signal to shift the individual towards a pattern B LDL profile [48, 49]. Ultimately, the connection of dyslipidemia to hypertension is thought to be through the reduced diameter of blood vessels due to the accumulation of the lipids in the blood vessel walls, leading to atherosclerosis. (The actual process requires at more essential events, described below.)

Neurological Disorders

Just 20 years ago, medical texts listed the brain as an insulin-insensitive organ. Since then, we've had an explosion in research detailing the myriad and diverse processes in the brain that are regulated by insulin. Indeed, the brain is very responsive to insulin; insulin plays a role in regulating appetite and energy expenditure at the brain, as well as altering reproductive hormones from the brain (explored later) [50]. In particular, insulin is sensed in the arcuate nucleus of the hypothalamus and alters brain biochemistry in such a way that insulin will signal that brain to reduce appetite; thus, when the brain senses increased insulin, appetite will wane. Of course, this doesn't work as well when the brain becomes insulin resistant [51]. Arguably more important than its effects on body weight and metabolic function are insulin's actions on memory [52], which makes it particularly relevant to the handful of chronic degenerative brain disorders. When we talk about insulin resistance, it's tempting to only think of a few tissues becoming insulin resistant, like the muscles or the liver. However, more and more, we appreciate that the brain becomes insulin resistant concurrently with the rest of the tissues. Not only can this drive obesity (i.e., less responsiveness to insulin leads to less satiety), but also it can have profoundly negative effects on brain physiology, increasing the risk of developing severe brain-related diseases.

Cognitive Decline

Before highlighting specific brain diseases, it is worth mentioning that insulin resistance is known to reduce brain function [53]. Interestingly, at normal levels, insulin signaling in the brain plays a role in learning and memory formation [54]. One remarkable study in rats found that an experimental model of type 1 diabetes, wherein the animal can't make insulin, failed to learn a maze as well as control animals. However, upon giving insulin to the type 1 diabetic animals, their learning and memory improved [55]. All of this simply suggests the importance of insulin in normal brain function. Of course, problems arise when you have too much insulin and/or the brain fails to respond to insulin. In those conditions, short-term learning is compromised, and long-term brain function may begin to suffer [56]. Not only can this have important implications on our health and academic performance, but it also has serious implications with some prominent brain diseases.

At the heart of several of these insulin-brain disorders could be a simple state of the brain being less capable of using glucose for a fuel [57], including several of the disorders discussed below, such as Alzheimer disease [58] and migraines [59].

Alzheimer's Disease

Dementia is a term referring to a loss of memory and intellectual function that compromises daily life. Among the few disorders that qualify as dementia, Alzheimer's disease is the most common, accounting for up to 80% of all dementia cases and affecting roughly 30 million people worldwide [60]. If current trends continue, this number is expected to double every 20 years [61]. Despite its prevalence, we still only vaguely understand the disease—both diagnosing it and treating it, not to mention preventing it. What's becoming increasingly clear, however, is the truly remarkable contribution of insulin resistance to the disease.

Interestingly, physicians and scientists have been aware of the Alzheimer-insulin resistance connection for decades, though these early observations were thought to be a result of the relatively sedentary lifestyle of patients with Alzheimer's disease. As evidence continued to support the connection, and additional inquiry revealed that early-stage Alzheimer patients, despite having similar levels of physical activity and overall lifestyle as healthy non-Alzheimer patients, nevertheless were more insulin resistant, the connection became harder to ignore.

Alzheimer's disease is a complicated disorder that undoubtedly involves mechanisms we're not yet aware of. However, a consensus has formed around the idea that two main features of the disease are the accumulation of plaques in the brain and the overstimulation of a neuron-regulating protein.

First, in Alzheimer's disease, the brain accumulates plaques known as amyloid β—clusters of protein bits that disrupt may healthy brain function, including memory, mood, motor function, and learning. Because these amyloid β plaques are so pathological, we have built in processes that help prevent them from building up. The most prominent mechanism that helps prevent these plaques from forming is ApoE—ApoE is a lipoprotein that enhances the degradation of these plaques. However, roughly 15% of all people have a version of ApoE known as ApoE4, which fails to perform this anti-plaque duty as well as normal. Consequently, people with ApoE4 are roughly 10-30 times more likely to develop Alzheimer's disease by their mid-70s [62]. Because of this, when studies have explored risk factors for getting Alzheimer's disease, having ApoE4 is always the most significant variable. Insulin may have direct actions on amyloid β plaque accumulation. Creating an artificial and acute hyperinsulinemia by infusing patients with insulin increases amyloid β in cerebrospinal fluid, with the results being more dramatic in elderly patients [63]. But producing amyloid β alone may not be sufficient to affect Alzheimer's disease risk; location matters. With Alzheimer's disease, amyloid β plaques accumulate in the spaces between nerves in the brain, not in the nerves themselves. And sure enough, insulin increases amyloid β release from brain nerves [64] increasing its accumulation outside and between the cells in the brain.

Second, tau is a protein that acts to maintain normal nerve structure. With Alzheimer's disease, tau becomes hyperactive and, like a rambunctious child, somewhat frenetic. Unfortunately, this state results in tau not doing its job as well; as opposed to maintaining nerve structure, tau is now tangling the nerves, creating neurofibrillary tangles, a second key feature, like amyloid β, of Alzheimer's disease. Normal insulin signaling in the brain inhibits the activity of tau [65]. Thus, in states of compromised insulin signaling (i.e., insulin resistance), tau becomes overactive, potentially leading to neurofibrillary tangles [66].

A research group in Finland performed a cross-sectional population-based study on risk factors of Alzheimer's disease [67]. They included the expected variables, as well as some unexpected variables. Unsurprisingly, having the ApoE4 phenotype was the most highly significant variable in people with Alzheimer's disease ($p=0.0001$, for those readers who care about the statistical strength). Other significant variables included age ($p=0.005$) and education level ($p=0.002$; a secondary benefit of attending school, although this may largely be a function of simply keeping one's mind active and frequently challenged [68]). Altogether, ApoE4 phenotype was the most highly significant variable. After that? The next most significant variable wasn't hypertension ($p=0.31$). It wasn't who had had a stroke ($p=0.59$). It wasn't smoking status ($p=0.47$). It was fasting insulin ($p=0.0005$). That's right—your fasting insulin is even more significant in your risk of developing Alzheimer's disease than your age!

Remarkably, every single marker of insulin resistance in this study was statistically significant with Alzheimer's disease, including abnormal glucose tolerance (p=0.003), fasting plasma glucose (p=0.031), two-hour plasma glucose (p=0.002; this measures blood glucose after the patients ingests a glucose solution), and two-hour plasma insulin (p=0.013).

The striking association of insulin resistance and Alzheimer's disease is so strong that Alzheimer's disease is occasionally referred to as “type 3 diabetes” [69]. This sentiment is supported by robust epidemiological and biochemical evidence [70]. Like every cell in the body, brain cells have insulin receptors—they sense and respond to insulin, which helps maintain normal brain cell function. An obvious effect of insulin at the brain is to stimulate glucose uptake [71], but other functions are just as critical and include brain cell growth, survival, and function [72]. Moreover, actual brain structure requires healthy insulin sensitivity; the brain is physically altered with prolonged insulin resistance. A recent study found that for roughly every 10 years of insulin resistance, the brain looks two years older than the brain in an insulin-sensitive person of the same age [73].

Reproductive Disorders

For the good of any species, reproduction is a function of every living thing. The primary regulatory steps in reproduction are hormonal, involving hormones that come from the gonads (i.e., testes in men, ovaries in women), as well as the brain. The brain and gonads interact in order to properly orchestrate the many events in the male and female that must happen to allow reproduction. But you'd never guess that a humble hormone from the pancreas could play such an important role as well.

The connection between insulin resistance and reproductive disorders may be the most unexpected disorder we cover. After all, everyone knows that insulin controls blood glucose, and maybe others know that insulin regulates other metabolic processes. However, most people would never imagine that insulin plays any role in reproduction, let alone an essential role; insulin is absolutely necessary for normal reproduction. The necessity of insulin in reproduction may be evidence of a simple yet profound link between metabolic and reproductive function. Reproducing is risky business—it wouldn't be prudent to bring offspring into a dangerous or unhealthy situation, such as a period of starvation. Insulin, then, acts as a signal for the brain that indicates the overall environment—normal insulin levels suggests the potential parent is healthy and eating a diet that is sufficient for growth of a fetus and even raising the newborn.

The necessity of insulin in reproduction is clear; experiments with rodents reveal that lack insulin leads to changes in brain and gonad function that decrease reproductive processes [74, 75]. But, too much insulin is no better than too little. Remember that insulin resistance is almost always a state of hyperinsulinemia—the pancreas is producing more insulin than normal in an effort to increase insulin's actions. Insulin-resistant men [76] and women [77] are more likely to be infertile than their insulin-sensitive counterparts. Additionally, insulin-resistant children are more likely to experience alterations in puberty [78].

Polycystic Ovary Syndrome

Polycystic ovary syndrome (PCOS) is the most common cause of female infertility, affecting approximately 10 million women worldwide. As the name suggests, the ovaries of the affected woman become burdened with cysts, resulting in highly painful ovaries that grow to several times over normal. At its very core, PCOS is a disease of too much insulin, an inseparable and causal factor.

Female fertility is a complicated orchestra of hormones, involving brain structures (i.e., the hypothalamus and pituitary) and the ovaries. For ovulation to occur, the prototypical event with female fertility, one of several developing follicles must become dominant and is subsequently released ("ovulation"). This sends a hormonal signal to the remaining follicles that cause their degradation and they subsequently disappear from the ovaries. The precursor event to ovulation is a massive increase in estrogens from the ovaries, which then increases luteinizing hormone (LH) from the brain. Ultimately, these fluctuations allow the one follicle to become dominant and eventual ovulation. In the absence of this process, multiple follicles develop, with none becoming dominant. Thus, ovulation fails to occur, and the ovarian follicles linger and accumulate.

Ovaries, like any tissue, respond to insulin. Perhaps one of the more unexpected responses of the ovaries to insulin is the inhibition of estrogen production. In their beginning, all estrogens were once androgens; estrogens are created from androgens, such as testosterone. This process occurs in males and females for all estrogen production. But too much insulin inhibits the enzyme aromatase, which is the critical mediator in this process—aromatase is the enzyme that converts androgens into estrogens. But as its actions are dialed down because of excess insulin, androgens fail to convert to estrogens at the necessary levels, and estrogen production becomes lower than normal [79, 80].

Estrogen has countless effects throughout the body, but few more obvious in the female than its role in the menstrual cycle. Ovarian estrogen production increases dramatically around midway through the cycle. This bump positively feeds back to the brain, which increases the level of luteinizing hormone production from the brain. Luteinizing hormone is the final step in telling the ovarian follicles to mature and, in the end, for one follicle to become dominant, resulting in ovulation and the eventual degradation of the other developing follicles. If this mid-cycle estrogen bump doesn't happen, ovulation doesn't happen, and the ovaries retain and accumulate the follicles.

Independent of insulin's effects on ovarian estrogen production, insulin may also directly act on the brain to block normal luteinizing hormone production [81]. Luteinizing hormone production in the brain usually comes in pulses—periods of increased then decreased production. Insulin appears to prevent this pulsatile pattern, which may disrupt normal fertility.

The effects of insulin-induced sex hormone alterations have additional effects than just a failure to ovulate, which is mostly a consequence of reduced estrogens. Insofar as PCOS is associated with relatively fewer androgens being converted to estrogen, androgen levels are too high with PCOS. A normal action of androgens in males and females is the expression of body hair—higher androgens typically leads to more and coarser body hair; this usually results in increased facial hair on women with PCOS. Further, the increased androgens can cause typical male-pattern baldness in the woman as well. Lastly, the hyperinsulinemia alone, independent of sex hormones, often increases the presence of dark skin patches called acanthosis nigricans, a common feature of PCOS.

Male Reproduction

The primary problem with male infertility is low sperm counts or poor sperm quality. Secondary problems, which occur much less frequently, often include anatomical problems or genetic defects

Erectile Dysfunction

Men with insulin resistance have an increased risk of erectile dysfunction [82], and erectile dysfunction gets worse as the insulin resistance gets more severe [83]. Indeed, the relationship is so tight that erectile dysfunction could be one of the earliest signs of insulin resistance, with scientists recently stating in a research article that "...insulin resistance may be the underlying pathogenesis of ED in young patients without well-known etiology." [84] In other words, if a seemingly healthy young man has erectile dysfunction, insulin resistance could very well be the cause. But to appreciate this connection, we need to go back to the powerful influence insulin wields on blood vessels.

Erectile dysfunction typically stems from a problem of blood vessel regulation—blood vessels must dilate dramatically to develop and sustain an erection. This process requires the production and actions of nitric oxide, a chemical that potently dilates blood vessels [85]. As discussed earlier, as endothelial cells (the cells that line the walls of the blood vessels) become insulin resistant, they produce less nitric oxide, which deprives the blood vessels of a strong dilating signal.

The two essential components of lifestyle that encompass the risks of insulin resistance are what we do and what we eat—in other words, exercise and diet. Before you groan at the lack of originality in this statement, and before you put your head in your hands in fear of the perceived discipline and patience required for such changes, know that changing your physical activity and the foods you eat does not need to be the harrowing experience you might have felt before. In the context of insulin resistance (and the many diseases stemming from it), when it comes to diet and exercise, what you think you know may be wrong and what you might have tried before probably wasn't as helpful as you think.

At its simplest, the battle of thought between political agenda and scientific process in understanding ideal nutrition for good health was waged around the relevance of calorie number vs. calorie type. Supporters of calorie number argue that it's all a matter of mathematics—if you eat fewer calories than you expend, you'll be lean and healthy; if you eat more calories than you expend, you'll be fat and unhealthy. Advocates of the idea that the type of calorie is more relevant than the number contend that the nutrient, once consumed, elicits an effect on hormones in the body, particularly insulin, and that it's this subsequent insulin effect that drives insulin resistance, fat gain, etc. Thus, a key strategy with each school of thought is to either restrict calories, which invariably means a low-fat diet, or to restrict certain types of carbohydrates, which aims to keep insulin low. However, in addition to exploring this debate, there are additional dietary angles worth discussing, including fermented foods, fasting, and more.

Intermittent Fasting/Time-restricted Feeding

A common thread among many dietary plans is timing and frequency of eating. There are countless ways of manipulating eating time and frequency that range from compressing periods of eating to two or three meals per day, with substantial time gaps in between (i.e. time-restricted feeding), or other strategies that suggest eating normally for a few days, then avoiding food entirely for a few days (i.e. intermittent fasting). On the other end of the spectrum, some diets encourage eating several meals throughout the day (i.e, "grazing"; 6-8 small meals per day).

Because elevated insulin is one of the most, if not the most, relevant factor in developing insulin resistance, a highly rational strategy is to follow a dietary plan that incorporates periods of time throughout the day wherein insulin is kept low. This philosophy immediately suggests that frequent eating is less effective than less frequent eating—indeed, three meals per day is better than six [86]—but are fewer meals than three best of all? Maybe.

Time-restricted feeding and intermittent fasting strategically include periods of deliberate food avoidance. The evidence regarding its efficacy in improving insulin sensitivity is valid, though it partially depends on how it's done. Two studies used this idea by having study subjects eat normally one day (i.e. unrestricted) and essentially fast the entire second day (i.e., alternate-day fasting), repeated seven times over a two-week period and found conflicting results—one reporting an improvement in insulin sensitivity [87], while the other observed no benefit [88]. An alternative strategy, wherein the person confines eating to a specific window of time each day (e.g., eating breakfast and dinner only [89] or lunch and dinner only [90]) yielded robust improvements in insulin sensitivity.

A critical distinction must be made between thoughtful food restriction and starvation. Whereas fasting and time-restricted eating is a deliberate restriction of food daily (i.e. time-restricted eating) or for longer (i.e. intermittent fasting), each is a scheme that involves eating fully for some period of time, with deliberate restriction for only certain periods—part of a day each day or an entire day every so often. There is ideally no calorie counting with either strategy—simply avoiding food certain times and eating normally (until satiated) other times.

It may seem like splitting hairs, but there's an important yet fine line between eating to keep insulin low vs. starving your body. Taken to an extreme, it's possible fasting can do more harm than good. There is no definite time past which fasting becomes harmful, so much depends on the constitution of the person fasting, how they define "fasting" (e.g. what are they drinking, how are they supplementing, etc.), and how they're compensating for not eating essential minerals (e.g. magnesium). Importantly, early studies into prolonged fasting found a potentially lethal consequence can develop after fasting ends, termed "refeeding syndrome" [91]. And, if not done smartly, prolonged fasting becomes actual starvation, which can paradoxically cause the body to become insulin resistant [92].

The elephant in the room with studies exploring time-restricted eating or intermittent fasting is the macronutrient content of the diet. (To my knowledge, these studies have yet to be performed.) Altering the macronutrients of the diet (e.g., carbohydrates vs. fats) may yield disparate responses not only with how well the individual can maintain the diet, but also whether it's healthy. Whether it's feasible and sustainable are affected predominantly by the amount of calories consumed; if a person fasts ~18 hours each day (i.e., eating from noon to 6 PM), whether this is healthy will depend on what they eat when they do eat. By consuming more of one macronutrient over another, the person may ensure they're providing sufficient energy to the body, despite eating less total amount (i.e., volume) of food, which means increased satiety [93]. Energy (e.g., calories) from a meal conveys greater satiety than bulk—if your cells are fed, they don't care whether there's something in your stomach.

For better or worse, studies that have explored restricted eating view it, at least in part, as a strategy to keep calories low rather than keep insulin low—the two ideas are not, or need not be, the same. As we'll discuss now, calorie type is at least as important as calorie number.

Carbohydrate Restriction

Once we appreciate that too much insulin is a main driver of insulin resistance, the chain of events suggesting a solution is too obvious: eat fewer carbohydrates=reduced blood glucose=reduced blood insulin=improved insulin sensitivity. With a lowering of insulin comes a sort of resetting (re-sensitizing) of the "insulinostat". Without doubt, controlling insulin leads to improved insulin resistance [94, 95].

Dietary protein elicits a mild insulin effect (about 2-3 times above normal, although somewhat variable), carbohydrate can elicit a remarkable increase in insulin (>10 times above normal; highly variable depending on the carbohydrate), while dietary fat elicits no effect at all [96]. Thus, a diet that restricts the insulin spiker (carbohydrate) and increases the insulin dampeners (protein and fat) is one that will improve insulin sensitivity. And it does.

In a grand historic perspective, it is somewhat common to hear some claim, while acknowledging the evidence in favor of carbohydrate restriction, that this is a fad or that it is otherwise a novel and thus poorly understood strategy. Indeed, several of the studies we will cite below include statements such as: "carbohydrate restriction resulted in greater improvements in [insert outcome here], but the long-term effects of such a diet are unknown." This is amusing in a historical context; the historic precedent in support of carbohydrate restriction can be appreciated in two periods—ancient and modern.

Over the millennia that passed from early man until now, the greatest change in eating came from the establishment of agriculture and the subsequent shift in nutrients from a diet high in fat to one high in carbohydrate. Restricting carbohydrates was perhaps the first modern documented intervention to control diabetes and weight and was accepted as fact throughout Western Europe in the early and mid 1800's. Why such a paradigm fell out of favor and was replaced with the current recommendations that those with insulin resistance and type 2 diabetes avoid fat and eat starches is puzzling, but the shift in guidelines was dramatic. Within decades (from the early to the mid 1900's), guidelines for diabetics went from encouraging strict avoidance of bread, cereals, sugar, etc. while allowing any meats, eggs, cheese, etc. (per The Practice of Endocrinology in 1951), to just the opposite—encouraging breads and cereals while discouraging meats, eggs, etc. (per the American Heart Association and American Diabetes Association). We responded—we eat relatively less fat now than perhaps ever before and certainly less than we ate 50 years ago [97].

The explosion of insulin resistance at home and abroad is evidence that the dietary shift has not yielded the intended results. Clinical research over the last few decades has provided abundant evidence that carbohydrate restriction is a superior dietary intervention to prevent or improve insulin resistance. Indeed, when comparing studies that are intervention or clinical based, rather than prospective or questionnaire based, the consensus is overwhelmingly supportive of carbohydrate restriction. Intervention-based studies are far superior because they're able to definitively answer questions, such as "which diet is best for improving insulin resistance?" One study that asked this question brought in hundreds of overweight middle-aged men and women. For two years, study subjects were assigned to one of three diets: a calorie-restricted low-fat diet, a calorie-restricted moderate-fat diet, and a non-calorie-restricted low-carbohydrate diet. In addition to causing the greatest weight loss, the non-restricted low-carbohydrate diet also helped lower insulin and improve insulin resistance the most [98]. A different study employed a similar strategy for 3 months, wherein overweight men and women were split into either a low-carbohydrate or low-fat diet group, both calorically non-restrictive. While insulin levels dropped by roughly 15% in the low-fat diet group, subjects in the low-carbohydrate diet group saw insulin levels drop by 50% [99]. Moreover, the HOMA score, an index of insulin resistance, dropped over three times more with the low-carbohydrate diet compared to the low-fat diet.

One final study worth mentioning followed study subjects for almost four years while they adhered to a carbohydrate-restricted diet [100]. The thrust of the study was to compare metabolic improvements, including insulin sensitivity, with two interventions—diets containing either 50% or 20% carbohydrate. Not only was the lower carbohydrate diet "significantly superior" at improving health, it ultimately led to almost half of the patients getting off insulin (and almost entirely off any other medications) and the rest substantially reduced daily insulin requirements. A final study worth mentioning here is one that put insulin-resistant subjects on a relatively normal diet (~60% carbohydrate) or moderately restricted with carbohydrates (~30%) for three weeks then switched over to the other diet for another three weeks. Once again, insulin sensitivity increased more with the lower-carbohydrate diet [101].

There are many, many more studies that indicate similar results establishing the efficacy of diets low in carbohydrates to remarkably improve insulin sensitivity. To help sum up this fact, multiple meta-analyses that pool the findings from dozens of studies, encompassing thousands of patients, unanimously reveal that a carbohydrate-restricted, calorie-unrestricted diet lowers insulin at least as much and often more than low-fat, calorie-restricted diets [102, 103].

Importantly, the collective evidence supporting carbohydrate restriction should be viewed in the context of insulin and, thus, should not be considered a call to avoid all carbohydrates. Not all carbohydrates are created equal and whether they are considered "good" should depend on the degree to which the food increases insulin.

Carbohydrate Quality vs. Quantity

I encourage thinking of carbohydrates as being on a spectrum with regards to their effects on glucose and insulin. A useful tool in deciding whether a carbohydrate is "good" or "bad" is by determining its glycemic load (NOT glycemic index)—a number that estimates how much an actual food will raise a person's blood glucose. Convention has it that a GL of 20 and above is "high", 11-19 is "moderate", and 10 or below is "low"; and this convention is fine, just remember: the lower the better. Thus, it's possible to consume a diet that has a higher amount of carbohydrates and still potentially prevent or improve insulin resistance if the nature of the carbohydrate is such that it's considered having a low GL. A good example of this is fiber.

In insulin-sensitive subjects, a diet high in fiber (and subsequently higher in carbohydrates) improves insulin sensitivity [104, 105]. However, a similar study using overweight, insulin-resistant subjects observed no such benefit [106]. Such disparate observations may be a result of carbohydrate tolerance—some people respond more negatively to carbohydrates than other people. Importantly, for people with insulin resistance, keeping the glycemic load low is significantly more effective at improving health compared with a low-fat diet [107]. Of course, as a reminder, the underlying utility in understanding the glycemic load is to get an idea of what the food is doing to insulin.

The other mechanisms that create insulin resistance, such as oxidative stress and inflammation, are also improved with a diet that is lower in carbohydrates [108, 109]. Thus, carbohydrate restriction addresses several, and the most impactful, of the distinct causes of insulin resistance. However, avoiding insulin-spiking carbohydrates have other effects that help improve insulin sensitivity as well.

The specific composition of macronutrients (i.e. the percent of calories from fat, protein, carbohydrate) can vary, but a constant feature is that carbohydrates constitute a far smaller part of the diet than is typical. This is a far cry from our conventional and ubiquitous "Western diet" (~50-60% carbohydrate), but that's a good thing—we're looking to reverse the trends this diet brought on. Unfortunately, due to inherent metabolic differences among all people, it simply isn't possible to establish a one-size-fits-all strategy with splitting up macronutrients.

How to Implement

If you answered "yes" to two or more questions from the "Insulin Resistance Quiz" at the beginning of the book, you're less tolerant of carbohydrates and, therefore, will need to be more cautious of the type and amount of carbohydrates you eat. If you answered "yes" to only one or none, you'll have more room for carbohydrates in your diet. The reasons for this spread are simply due to how likely it is your body will need make more insulin, and keep insulin higher for longer, in order to clear the glucose from your blood following the meal. Remember that while carbohydrates have a robust increase in insulin (though there is a broad range; broccoli has little effect, while potato chips have a large effect), protein will have a modest effect, and dietary fat will have none. With this in mind, here are some general macronutrient ranges (percent of calories from fat-protein-carbohydrate) that may be helpful as you plan a new nutrition plan to improve or prevent insulin resistance:

1. If you answered "yes" to two or more: ~75-20-5
2. If you answered "yes" to one: ~70-25-5
3. If you didn't answer "yes" to any questions (and never want to): 60-20-20 or 60-25-15 (or higher, as warranted)

Keep in mind that these ranges may require some optimization on your part—these numbers are not meant to "final". Try it out and modify as needed. The protein levels can be increased as needed, without too much effect on glucose and insulin (more on this below), and may need to be increased based on physical activity and age (we need more protein as we age; more on this below).

If you're determined to improve your insulin resistance, you may benefit from purchasing ketone test strips. You'll recall that a diet that keeps insulin low will also increase ketone production from the liver; this process of ketogenesis is a normal, even healthy, state where the body is using fat at such a high rate that some of the fat is being turned into ketones. Most of the ketones will be used by the body, especially brain, for energy, but some are lost in our breath and in our urine. Because of this, you can measure your ketone production by measuring ketones in a number of ways. The most accurate, and most expensive, is to purchase blood ketone test strips. The cheapest method is purchasing urine test strips. A final method is a breath ketone analyzer (i.e. ketonix). All have pros and cons that you can consider when deciding whether to take this route. Many people find it highly motivating to measure ketones in order to determine how well they're doing with lowering insulin through dietary changes. Unfortunately, until an at-home method of measuring insulin is available, this is the easiest way to get an idea of insulin (albeit inversely).

One thing for all to keep in mind: you don't need to be constantly in ketosis to enjoy its insulin-sensitizing benefits. Undoubtedly, measuring ketones is an effective (and motivating) way to ensure insulin is consistently low, but simply having prolonged periods during the day where you're eating and living in such a way that glucose and insulin are low is a wonderful and healthy step in the right direction. To this end, I recommend adopting a simple strategy of time-restricted feeding in some form. I've found a simple and effective method for this is to ensure you have a 12-hour period each day of no eating (but water is fine). Usually, this will take the form of eating dinner around 5-7PM and not eating again until 5-7AM or so. Additionally, I recommend extending this to an 18-hour fast two to three days per week (e.g., dinner at ~6p and lunch at noon the following day). If it's difficult at first, you'll be surprised at how quickly it gets easier, especially when your meals are higher appetite-sustaining fat.

As a general rule: be smart about meal replacement shakes. Most, with the best of intentions, are filled with insulin-spiking ingredients. Look for shakes that are built on proteins and fats —not only are they the essential macronutrients, but they'll have the least effect on insulin (if any). Also, the sources of these proteins and fats a great deal. For proteins, nothing beats those from animal sources, such as whey and egg whites. For fats, anything from animal (e.g., butter/ghee, etc.) or fruits (e.g., coconut, olive) are best.

As you embrace nutritional changes to become more insulin sensitive to help control body fat and disease risk, I believe there are four vital pillars that provide the foundation of a smart plan:

1. Control carbohydrates: This is the first and fundamental principle to rapidly and effectively controlling insulin. I'd suggest the following amounts, depending on the Insulin Resistance Quiz:

    a. If you answered "yes" to two or more: ~0-50 grams/day.
    b. If you answered "yes" to one: ~0-75 grams/day.
    c. If you didn't answer "yes" to any questions (and never want to): ~0-100 grams/day

Along with this general idea of controlling carbohydrates, here are some addition thoughts to consider:

- Don't be so sweet! An insulin-sensitizing nutrition plan will have very little sugar in it. A large part of this is to recognize that sugar is ubiquitous in its many forms. Whether it's "cane sugar", "evaporated cane juice", "high-fructose corn syrup", "brown rice syrup" or more, they're all the same garbage. You can find sugar-free versions of the most common foods in your home, paying particular attention to things like sauces, dressings, ketchup, peanut butter, etc. Who wants sugar in these foods anyway, right? You won't taste the difference. When it comes time to actually enjoy a dessert, I encourage you to limit this to only one treat per week or find a way to make or purchase versions with fewer carbohydrates.

- Be starch smart! Carbohydrates are an incredibly diverse macronutrient and the more natural the carbohydrate, the better. A general rule to help avoid the worst of the carbohydrates is that if it comes in a bag or a box that sits on a shelf, it's likely a carbohydrate to avoid. And don't drink your carbohydrates. Where you're able, make an effort to focus on more fermented carbohydrates, like raw sauerkraut, kimchi and apple cider vinegar.

2. Prioritize protein: Avoid the temptation to eat too little protein; one of my concerns as people adopt a low-carbohydrate, high-fat diet is that they excessively eschew protein (such as meat). While certain amino acids (the parts of the dietary protein that flow in the blood) can elicit an insulin effect, the degree to which insulin increases in response to the amino acid depends heavily on the degree to which a person is ingesting carbohydrate (i.e., the level of blood glucose). If carbohydrate consumption is low, there is little or no insulin response to dietary protein. In contrast, if carbohydrate consumption is high, and blood glucose is elevated, there is a substantial insulin response to dietary protein [95, 110]. To optimize muscle and bone growth and recovery, aim to get 1-2 grams of protein per kg [111]. Critically, if you're older, you need to be on the higher end of this; we become increasingly less capable of dietary protein into muscle protein as we age [112].

3. Don't fear fat: Embrace the insulin-sensitizing value that comes from eating real foods with all their glorious fat. Remember that fat, does not increase insulin and is, thus, a useful food that can nourish your body while not feeding the beast (i.e., insulin resistance). In fact, be wary of meals that don't include fat; they won't have the ability to satisfy as much and the insulin effect of the meal will very likely be higher than it would otherwise be. Also, challenge the dogmatic definition of "healthy fat"; the more unsaturated a fat, the more readily the fat is oxidized (and thus harmful) and likely containing unwanted chemicals from the processing of the fat. Thus, saturated fats from animal and fruit sources (i.e., coconut, olive, avocado) are ideal.

4. Watch the clock! Fast from food (not water!) for 12 hours every night and 18 hours two to three days per week (e.g., eat dinner at 6PM and eat your first meal at noon the next day). If your meals are higher in fat and lower in refined carbohydrates, you'll be surprised at how easy this becomes as your body adapts to using fat, including your own body fat, as a fuel. Every two to four weeks, go all the way and fast from food for 24 hours.

Do something now.

1. Eat better! Change your breakfast tomorrow (and everyday thereafter) to one that avoids sugars and refined starches and, rather, includes fats and proteins from real foods. As you can, change other meals.
2. Get your insulin measured! Most clinics can measure insulin (albeit by request only); if your insulin is above 6 µU/ml, make a change. If your clinician is agreeable, go a step further to measure insulin during an oral glucose tolerance test; if your insulin is above ~60 µU/ml at 30 minutes or above ~30 µU/ml at 2 hours, make a change. [If you can't easily measure your insulin, there are a couple alternatives: 1. Measure your blood pressure. If you've managed to lower your insulin levels, blood pressure should come down within a few days; 2. Measure your ketones. By purchasing a ketone meter, you can get an idea of insulin control, insofar as ketones will start to rise as insulin starts to come down. This may take a few days, as well.]
3. Get help! Share some of these relevant studies mentioned in the book with your doctor (he or she may know as little as you did about this!). Go further by including family and friends—teach them what you've learned about how serious the effects of insulin resistance can be, how it develops, and what you can do about it. Remember, statistics suggest they may have insulin resistance (or soon will).

My hope is that by knowing that all the chronic disorders mentioned in this book share a common origin (i.e. insulin resistance), you feel empowered to make a simple lifestyle change that helps reduce the risk of all of them. Because you can do something—your lifestyle, with your individual strengths and weaknesses, genes and circumstances, is a big part of what got you where you are and, if done right, can get you to where you want to be.

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