New Perspectives on Insulin
Contributing Influences on Body Fat and Insulin Resistance
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The search for weight loss has become an obsession of the Western world. As the calorie model has been refined to include hormonal influences of diet and exercise, new approaches have emerged. One of the major players in the new understanding of hormones and obesity is insulin. Insulin is now recognized as a powerful fat-storing hormone, which has led many weight loss practitioners to advise patients to lower their insulin levels as much as possible. Many different dietary approaches including Atkins, The Zone, and South Beach have emerged from this idea.

While controlling insulin is of utmost importance in decreasing excess body fat, a strict focus on lowering insulin levels may not always be the best approach. The thought in reducing insulin levels is that low levels decrease body fat and slow aging. Many studies in calorie restriction and the aging process have substantiated these conclusions.[1,2] However, the better approach may be to bolster insulin sensitivity, since this would also slow aging and have the added benefit of enhancing function at the same time. By reducing insulin to very low levels, gains in muscle mass may be hindered, and body function could be compromised, leading to energy imbalances like fatigue, depression, and sarcopenia.[3,4] Without insulin's fuel-regulating potential, we could be trading more years for less functional living.[5,6] By focusing on insulin sensitivity over simply lowering insulin levels, we may be able to deliver patients the best of all worlds.

Harnessing the potential of insulin while avoiding its downside makes it necessary to understand insulin and insulin resistance and what purpose each might serve in a historical sense. Appreciating the natural situation in which humans evolved provides insight into how to use insulin to our benefit when seeking fat loss. The idea that insulin resistance is always systemic is another issue that can help. Clinical tools that help determine where insulin signaling is deranged can be valuable in restoring insulin sensitivity. Glucose tolerance testing may be a useful tool in this regard.

By altering diet and exercise habits appropriately, fat-loss seekers can use insulin to gain muscle and minimize its fat-storing effects. This is the best of all worlds since insulin sensitivity or insulin resistance determines to a large degree which mechanism – fat storing or muscle building – will predominate. By shifting the focus to insulin sensitivity instead of just insulin reduction, both a longer and more functional life can be achieved. It seems a more intelligent approach, in which lifestyle and synergistic hormonal effects mediate insulin's actions and therefore could allow for insulin's muscle-building properties to be enhanced, while its fat-storing effects are reduced. These factors are the very same ones most associated with a long life and functional independence in old age.[6,7]

Insulin Resistance in a Historical Frame of Reference

Insulin resistance in combination with high insulin levels is a major contributing factor to obesity-related complications. Interestingly, insulin resistance does not merely occur as a result of high insulin levels.[8-13] Insulin resistance is also prevalent in starvation and catabolic diseases like anorexia.[9,11-13] Contrary to popular thought, insulin resistance can exist in the presence of low insulin levels as well as high insulin levels.[9-13] This begs the question: what exactly is insulin resistance doing in the body and how could both an overfed and starvation state induce it? If we look at it in the context of evolution, we would expect to find a survival benefit of insulin resistance.

Insulin resistance is related to survival especially in free-living mammals that are preparing for hibernation.[14] It would make sense from an evolutionary construct to develop physiological systems that could maximize the resources at hand to help in survival. For this to make sense, there would have to be evidence of this in wild animals. Animals like bears, squirrels, and other mammals show insulin resistance similar to humans, beginning in the summer months and progressing as they near hibernation.[14-15]

Insulin and the Seasons

The seeds of insulin resistance in mammals may be planted in the summer months when food is plentiful and insulin levels begin to rise. During this time of the year, the days are long and animals are very active, so the higher insulin levels promote both fat gain and the maintenance of muscle mass. As late summer drifts into fall, insulin levels will rise further as more starchy foods become available in the form of fruits, tubers, and squashes. These calorie- and sugar-rich foods elevate insulin levels. At the same time, days are becoming shorter in the fall, causing a reduction in activity levels for non-nocturnal animals. Since the muscle mass of an individual determines 40% of his or her insulin sensitivity[16] and 70-90% of blood glucose clearance,[17] this lack of movement is substantial.

Decreased movement as well as a rich supply of high-carbohydrate plant foods would greatly impact insulin sensitivity. This combined with higher-than-average insulin levels would lead to a hyperinsulinemic and an insulin-resistant state. The combination of hyperinsulinemia and progressing insulin resistance is the perfect scenario for fat storing, assuring all calories consumed would be preferentially stored rather than burned immediately for fuel. In the face of an approaching winter, there is no doubt this would have provided a key survival advantage.

The rich supply of food present in the summer and fall would come to an abrupt halt in winter. In prehistoric days, winter was a time of starvation with very few food resources available. This drastic reduction in calories would act as a primer for human physiology. Maintaining insulin resistance through the winter could serve as protection. Insulin's action on the liver is to blunt hepatic sugar production (gluconeogenesis), but during times of starvation and fasting, this is exactly what you need. By maintaining insulin resistance at the level of the liver and fat, the body would be unimpeded in its ability to use stored fat and muscle protein to make sugar.

Interestingly, low insulin levels and a persistence of insulin resistance characterize diseases of starvation-like anorexia.[9-10,18] One recent study has also demonstrated that an abrupt switch to a very low-calorie diet by obese subjects aggravated insulin resistance in those who already had it and actually induced it in those who did not.[18] This seems to lend credibility to the idea that insulin resistance is a physiological state that evolved as a survival mechanism; however, if the fluctuation in seasonal availability of food is a predictor of insulin levels and sensitivity, then we might also expect to see a relationship of insulin to light, sleep, and activity. It is already a well-established fact that exercise and movement are highly correlated with insulin sensitivity, but the associations with light and sleep are less well known.

Insulin, Light, and Sleep

The natural rhythm of light and dark cycles dramatically impacts physiology but is unappreciated in most discussions of insulin. The seasonal variation in temperature and light exposure influences physiology directly and indirectly. It has been shown that both short-duration sleep and long-duration sleep are positively correlated with insulin resistance.[19-20] In the natural world, the summer months are marked by long days and short nights, effectively shortening the time the body would sleep. At the other end of the spectrum, winter exposes the physiology to the opposite effect: long nights and short days.

As hinted above, it would be beneficial to cultivate some degree of insulin resistance in both these seasons for survival. In the late summer and early fall, a hyperinsulinemic and an insulin-resistant state would be a perfect adaptation towards storing fat for the coming winter. In the winter, a hypoinsulinemic state along with insulin resistance would assure all resources available were mobilized to supply the body with energy to survive winter, during which food will be less available.

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The seasonal variation in light and day length also affects the food availability and exercise patterns, which strongly impact insulin sensitivity. Winter with its very short days means very little exercise and very little food. Summer means lots of exercise with lots of food. Fall therefore is the perfect scenario for enhanced fat storing (i.e., lots of food and declining exercise). By the same rationale, spring with its adequate food supply and vigorous movement patterns would have the opposite effect.

Several studies show that seasons influence insulin resistance and diabetes.[21-23] Weight gain in preparation for winter by animals parallels many of the same physiological changes seen in diabetes in humans.[23-26,29] In animals, this situation is acute and protective, but in humans, it becomes chronic and degenerative because the environment of the modern day has elements resembling summer and fall: reduced sleep, decreased movement, and abundant food. This leads to insulin resistance on a chronic continuous basis and eventually to type 2 diabetes.

The approach of almost all popular weight loss programs is to address obesity and insulin resistance by lowering calories. Unfortunately, this mimics a winter environment and convinces the body that its attempts

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at insulin resistance were exactly the right course of action. In response to decreased calories and insulin resistance, the body may become more insulin-resistant, not less.[18] Clearly, this course of action is not beneficial, especially in consideration of slowing thyroid function in the face of calorie restriction.

Insulin Resistance in Different Tissues

To develop a more complete approach to controlling insulin, it is important to look beyond the common belief that insulin resistance is always systemic. Tissue-specific insulin resistance is a more accurate description of what may be occurring in some people with insulin resistance.[27] The liver, muscle, adipose tissue, and even the brain and pancreas can all develop dysfunction regarding insulin signaling. Which tissue develops resistance has much to do with genetic and lifestyle variation. The important thing to understand is that just because a person has insulin issues in one tissue does not necessarily mean they have it in another.[27-30] In addition, the degree of systemic insulin resistance and the development of full-blown diabetes have much to do with which tissues lose insulin sensitivity.[30]

The research in this area is anything but conclusive. However, experiments on mice with insulin receptor "knock out" in certain tissues gives insight into which tissues are having the most dramatic impact on obesity and whole body fuel utilization.[30] It has been thought by some that obesity causes insulin resistance. However, recent research suggests this is not the case and that insulin resistance can be seen in tissues both in a starved and overfed state[10,18] and without elevation of adipokines.[28]

Muscle tissue may be the first tissue to begin to develop resistance to insulin very early in metabolic syndrome.[16, 31-33] This would lend credibility to the evolutionary aspects of insulin sensitivity and the development of increased fat depots for survival in winter. As movement decreased due to shortened days and dropping temperatures, muscle would necessarily lose its sensitivity. Since muscle is responsible for 70-90% of postprandial glucose disposal, that would begin to put a burden on the adipose tissue and liver.

The liver seems to develop the problem through several mechanisms including local defects in lipoprotein lipase (LPL) function,[2] visceral adipose tissue,[38] and/or compromised glycogen storage in the muscles.[32] Adipose tissue sensitivity is tricky, with visceral adipose tissue behaving differently than subcutaneous adipose tissue.[35,37] One thing is certain, as adipose tissue grows, especially visceral adipose tissue, the insulin resistance syndrome is dramatically enhanced through fat cell-signaling molecules like TNF-alpha and other adipokines.[38] As fat tissue grows in response to increased food intake or decreased movement, hormones like leptin, resistin, and adiponectin will have direct impacts on other tissues' ability to properly interact with insulin. Liver and muscle tissues are keenly sensitive to these signaling molecules.

Some research suggests visceral adiposity secretes more resistin (decreases insulin sensitivity), while subcutaneous fat expresses more adiponectin (enhances insulin sensitivity).[34-35] This may allow the subcutaneous fat to remain more receptive to insulin as the visceral fat remains more resistant. This also highlights how different fat depots differentially impact systemic resistance to insulin.

Ironically, some studies on insulin resistance in peripheral fat shows there is actually a protection from obesity when peripheral fat becomes resistant to insulin.[37] From a fat storing point of view, resistance to insulin at the level of fat would result in less fat storage and more fat burning. This makes sense, since the role of insulin in fat is to decrease lipolysis in favor of lipogenesis. Mice with insulin receptors knocked out at the level of the fat cell show decreased fat storage and none of the defects associated with systemic insulin resistance like hyperglycemia and hypertryglyceridemia.[30]

Research is unclear as to which tissues are affected first and why, but it appears resistance at the level of the muscle and fat is less detrimental than resistance at the level of the liver.[30] When the liver loses its ability to respond to insulin, all the systemic effects like low HDL, high triglycerides, and fasting hyperglycemia begin to occur. It is likely these tissue-specific differences are based to some degree on genetics but obviously are impacted by the environment as well. The important thing would be to deal with the tissue that is most in need to slow the progression of the resistance. Some of the drugs used to treat metabolic syndrome already work in a similar fashion. Metformin's (Glucophage) mechanism of action seems to be working at the level of the liver, while PPAR gamma agonists like rosiglitazone (Avandia) seem to impact both peripheral and liver resistance.[39]

While this issue may seem to confuse the matter further, the understanding of this phenomenon can make a profound impact on the ability to restore insulin function. Knowing where the primary site of insulin resistance has developed allows practitioners to fully address that tissue. Recently, researchers have used glucose tolerance tests paired with insulin measures to pinpoint where insulin resistance is most centered.[33] They have used this technique as a way of distinguishing muscle from liver resistance. This study seems to suggest a quick and higher-than-normal rise of blood sugar in a glucose tolerance test, followed by a sharp decline, which would indicate resistance primarily in the liver since insulin's action on the liver is to blunt gluconeogenesis. Without insulin's action, a higher fasting and postprandial glucose surge would be seen. A moderate rise in blood sugar that stays elevated throughout the test

may indicate muscle resistance. This is because muscle is the primary mover of glucose out of the blood due to its rich supply of glucose transporters and would be the major factor in clearing blood through the course of the test. Of course, many people may exhibit a combination of the two, pointing towards insulin resistance in both areas.

Tissue-Specific Lifestyle Approaches to Insulin Resistance

Given this understanding, diet and exercise approaches can be developed to address the specific insulin defect involved. This would include not only whether to focus more on diet as compared to exercise, but also what type of diet and exercise program would be best. For example, a dietary approach would seem more significant as it relates to liver insulin resistance since high-fat, high-sugar diets speed the development of liver resistance.[33]

An exercise approach would be more important in muscle resistance since movement alone is valuable in reducing blood sugar levels. Also of note is that the type of exercise has different actions on different tissues. Recent studies have shown that resistance training strongly impacts both liver resistance and peripheral resistance, while cardiovascular exercise may focus more strongly on peripheral resistance. It seems this has much to do with the type of muscle fibers engaged.

Type 1 muscle fibers are the body's endurance fibers and are involved in endurance activities like running. Since type 1 (oxidative) muscle fibers are the richest source of the glucose receptor (glut4), they are excellent at reducing resistance in the muscle tissue.[41] Type 2 muscle fibers are involved in strength and power and are primarily activated in explosive sprinting and weight training. Type 2 (glycolytic)-dominated resistance training helps with muscle resistance as well, but also has interesting effects on insulin-related genes in the liver.[40]

A fascinating new study published in the February 2008 issue of *Cell Metabolism* shows that hypertrophy of type 2b muscle fibers has substantial and indirect effects on liver glucose metabolism. In this study, it was shown that growth of type 2b muscle fibers reversed insulin resistance induced on the liver by a high-fat, high-sugar diet. Of the 1200-plus genes involved in liver insulin resistance, simply the act of stimulating type 2 muscle fibers to grow was able to impact 800 or so of these genes to revert back to normal function. While the mechanism is not understood, the authors speculated that myokines (cytokines released form muscle tissue) might be playing a role.

Spring Time and Insulin Sensitivity

Controlling insulin-mediated fat storage becomes easier when both a historic frame of reference and tissue specific approaches are used. When considering the seasonal impact on insulin signaling, the spring environment would be most useful to emulate. In the spring, animals waking from hibernation have reduced fat and muscle tissue. Food is also becoming increasingly abundant and consists of young green plants and lean animals. The impetus to move is also extremely strong. Physical activity is constant as the search for food and the avoidance of becoming food requires perpetual motion.

The lean protein sources, abundant vegetable matter, and constant movement all create an environment of extreme insulin sensitivity. This could allow the body to quickly regain its muscle mass while remaining lean. The look of a modern-day athlete would seem most representative of what early humans in spring might look like. From spring into early summer, constant moving and foraging, along with intense bursts of activity to capture food and avoid becoming dinner, would continue to maximize muscle and minimize fat gains. This construct would seem to be most representative of human evolution. The scenario of abundant high-fiber and protein rich foods, combined with the movement patterns, would have forced insulin's actions into muscle building rather than fat storing. Other hormones elicited through the hypoglycemic diet and intense exercise would have also fostered the muscle-building action of insulin and countered its fat-storing effects. Taken together, the outcome would be robust health and optimal body composition.

Real-World Examples of Insulin Sensitivity

It is not a well-publicized understanding, but there are a group of people who have mastered the use of insulin and whose lifestyle closely resembles the springtime construct of early man. This population can literally burn fat at will and develop the leanest physiques in the athletic world.[42] This is because they use exercise and diet to maximize insulin's muscle-building potential while minimizing its fat-storing effects. These athletes are known as figure athletes, and they include bodybuilders, fitness competitors, and female figure competitors. This athletic population has been ignored largely because of the stigma associated with their sport. The common perception is that these athletes use performance-enhancing drugs. This is true of some in the professional ranks, but there is a much larger body of figure athletes who are completely natural. However, looking at the practices of both drug-free and drug-using figure athletes can be instructive for understanding the physiological action of insulin.

It is a well-established practice of drug-enhanced bodybuilders to use exogenous insulin to promote muscle gain. While the goals of these individuals may be questionable, it is interesting to note a population voluntarily increasing their insulin levels under the influence of an environment low in fat, high in protein, and with vigorous weight training. Contrary to what is seen with the overweight and obese, this population is able to achieve the leanest physique in the athletic world. ➤

Interestingly, this dual action of insulin can be seen in type 1 diabetics who either participate in activity and those who do not. The latter can become obese, while the former remain lean and muscular. Both kinds of type 1 diabetics demonstrate populations whose insulin regulation is under voluntary control. It is the strong influence of each diabetic's chosen lifestyle that determines whether they will be lean or overweight. The insulin-dependent diabetic who engages in intense physical training and pays close attention to diet remains insulin-sensitive, while the ones who remain sedentary and pay very little attention to food choices can and do become insulin-resistant.

Insulin sensitivity is mediated by environmental influences on not just insulin, but other hormones as well. It is important to remember that hormones act differently based on several factors: how much hormone is present, how sensitive the cells are to the hormone's action, and what other hormones are acting with it. Other hormones, including glucagon, growth hormone, and sex steroids, influence insulin sensitivity as well. When insulin is in balance with other hormones, it can be influenced towards muscle building while other hormones focus on fat burning. If the lifestyle factors that induce this state could be taught to weight loss clients, the outcomes would potentially be far better than simply telling people to lower insulin levels as much as possible. As we have seen, just because insulin levels are low does not automatically mean the tissues will be insulin-sensitive. It is really about regaining insulin sensitivity.

The Return to Spring

The lifestyle figure athletes employ is one that mimics the springtime of ancestral humans. They eat very lean protein sources including egg whites, chicken, turkey, and red meats. They also focus on lean and fatty fish. The carbohydrate intake is centered on vegetables, but they do not shy away from rice, potatoes, and oats. Their refined carbohydrate intake is non-existent.

The figure athlete's view of refined carbohydrates is somewhat different from that of most health care practitioners. They will avoid all breads, even whole grains, along with pasta and other wheat-based products. Fruit is also minimized. Milk and dairy also find limited application, except in the case of whey and casein-based protein powders. However, even these are eliminated completely when they near their events.

The calorie intake is rarely reduced except for short times right around competition. When analyzing the calorie intake of these athletes, it is interesting to see the emphasis is usually on making sure they are getting enough to eat rather than limiting food. This is largely due to the types of food they consume. Obviously a high, lean protein and vegetable-based diet with very little added fat will be very filling and lead to little concern about reducing calories.

Exercise too is unique. Unlike most people trying to burn fat, most figure athletes use cardiovascular exercise in a secondary fashion. Instead, weight training takes center stage in their exercise regime. We are now finding this to be unique in its ability to keep both the liver and muscle tissue sensitive to the effects of insulin.[40] When they do engage in aerobic exercise, it is usually of two sorts, either long-duration, slow-motion, walking-type exercise or intense and short, sprint-like exercise. There is a notable absence of long-distance, zone-type training among the vast majority of these athletes.

It is also interesting to note how these athletes are acutely aware of the synergistic effects intense exercise and insulin timing can have. While most of their meals are based on protein and fiber, these athletes often will carbohydrate and protein load post-workout. This will usually consist of a protein shake with a high-glycemic carbohydrate, like banana or honey. This practice has been shown in research to be highly beneficial in its ability to redirect metabolic processes towards glycogen synthesis and muscle building rather than fat storing.[44]

This lifestyle is one that very closely mimics the natural spring-time environment and is often seen in hunter-gatherer tribes living in climates that stay warm year-round. The activity level is extremely high with constant low-intensity activity through walking and then periods of short burst-type activity of lifting, hauling, and sprinting. The diet is also rich in vegetable, animal, and root veggies. This is also the chosen fare of figure athletes. This paleo-type diet has recently been shown to be superior in reversing insulin resistance when it is compared to the frequently prescribed Mediterranean diet.[43] While many patients are not trying to look like bodybuilders or figure athletes, the practices these athletes employ can be used to successfully reduce body fat in the average population.

Final Thoughts

The control of insulin and its resistance in different tissues is a primary factor in the ability to lose fat. However, insulin management is not as simple as attempting to lower insulin levels at any cost. Doing so sacrifices insulin's muscle-building potential and does not address the fact that insulin resistance can occur in both a hypoinsulinemic and hyperinsulinemic state. In addition, insulin resistance is not always systemic but can be tissue-specific. Understanding which tissue or tissues are involved can allow tailored exercise, diet, and supplemental approaches.

Unfortunately, weight loss approaches that focus on simplified models and ignore the historic context of human fat-burning physiology continue to dominate. Insulin resistance is not necessarily a disease state, but may actually be a highly sophisticated protective mechanism in times of famine as well as overfed states. Reframing the insulin question in the context of the natural world

helps us make more sense of the controversy and allows an approach that works with the body's natural constructs rather than against them.

When we combine the natural framework of insulin metabolism with modern-day populations who seem to have mastered insulin's action, we can begin to formulate meaningful fat-loss strategies. It is becoming increasingly obvious that the diet and exercise habits that figure athletes pursue are highly beneficial. Indeed, recent studies show weight training may have a distinct advantage in controlling insulin function in the liver and muscle tissue.[40] The Mediterranean diet, while exceedingly healthier than the standard American diet, was also recently shown to be far less effective than a Paleolithic diet including root veggies.[43] Ironically, these are the same approaches judiciously employed by figure athletes. As we move past the simple caloric model of weight loss into the hormonal model, insulin's role needs to be appreciated. By working to optimize insulin sensitivity rather than just lowering insulin levels, we may be able to drastically improve the metabolic conditioning of our patients.

Notes

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