An Interview with Gerald Reaven: Syndrome X : The Risks of Insulin Resistance

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Q: What is insulin resistance and how does it lead to Syndrome X?

A: It’s not as simple as it seems at first blush. Insulin resistance is the inability to regulate the action of insulin on muscle and adipose tissue. Insulin resistance, as it is measured, refers to insulin stimulated glucose disposal by muscle. The ability of insulin to regulate lipolysis in adipose tissue is also abnormal in patients who have muscle insulin resistance. The two defects are parallel in terms of magnitude, however, they are very different in their dose-response curves. For example, the circulating insulin concentration that would half maximally suppress lipolysis in adipose tissue is approximately 20 µ/ml. That is much lower than the dose of insulin that would half maximally muscle glucose disposal. The two organs have different dose-response curves. Therefore, the fundamental defect in patients with Syndrome X is insulin resistance in both adipose and muscle tissue.

In response to the insulin resistance, the pancreas tries to maintain glucose homeostasis, secreting as much insulin as it can to prevent the glucose levels from increasing. Syndrome X is, therefore, insulin resistance plus compensatory hyperinsulinemia, which prevents the evolution into type 2 diabetes. Manifestations of this are the complicated way the other organs of the body respond to the state of muscle and adipose insulin resistance and hyperinsulinemia. Many of the manifestations are not due to the insulin resistance per se, but to the fact that certain tissues remain normally insulin sensitive in the same individual who has muscle insulin resistance. An example is the kidney. The ability of insulin to stimulate sodium re-absorption by the kidney can be very normal at the same time that the muscle in that individual could be quite resistant to insulin action. The kidney is an "innocent bystander" of the increased insulin secretion in this person due to the muscle insulin resistance. Another example is the polycystic ovary syndrome, which is hypersecretion of androgens from the ovary in response to hyperinsulinemia. Hyperinsulinemia exists due to the muscle insulin resistance. The ovary, being exposed to consistently higher levels of insulin, increases its testosterone secretion accordingly, the ovary being insulin sensitive. It takes insulin resistance and compensatory hyperinsulinemia, to result in the various manifestations.

Q: How do the terms "the lipid triad" or "the metabolic syndrome" relate to Syndrome X?

A: The term "metabolic syndrome" is less preferable because many of the manifestations of insulin resistance are not 'metabolic'. For example, insulin resistance and compensatory hyperinsulinemia are associated with an increase in plasminogen activator inhibitor-1 (PAI-1), a factor which regulates the process of fibrinolysis. Would you consider this a 'metabolic phenomenon'? The word metabolic tends to take the focus away from the non-metabolic manifestations. Another name, "insulin resistance syndrome", implies we know that the basic defect is muscle and adipose tissue insulin resistance. I believe it is, however, others have suggested alternative first causes of the whole cluster of events. What the term "Syndrome X" does is leave us thinking about the fundamental defect without making any definitive decision. The phrase, "deadly quartet", implies that obesity is an essential component. That is just not the case. Obesity modifies how insulin resistant an individual is, but there are many very obese individuals who are quite insulin sensitive, who have nothing resembling Syndrome X.

Q: How does Syndrome X differ from type 2 diabetes?

A: Syndrome X and type 2 diabetes both have as their basic defect muscle and adipose tissue insulin resistance, however, type 2 diabetes develops in a relatively small number of individuals who are
insulin resistance. It occurs in those who are unable to secrete large amounts of insulin and therefore plasma glucose rises. On the other hand, most individuals who are insulin resistant continue to secrete large amounts of insulin and don’t get type 2 diabetes. At the time I made that distinction, I felt that the medical establishment didn’t quite understand the second half of this: that most insulin resistant patients did not get diabetes, yet were at risk for coronary heart disease.

Q. What are the signs of Syndrome X, and how can we as clinicians assess if individuals have this disorder?

A. The manifestations of Syndrome X can be broken down into six major categories:

1. Glucose intolerance: Individuals with Syndrome X don’t have diabetes, by definition, but their plasma glucose concentration is higher than those individuals who don’t have Syndrome X.

2. Dyslipidemia: The characteristic findings are high plasma triglycerides and low HDL cholesterol. The insulin resistance and compensatory hyperinsulinemia cause the liver to produce more triglyceride rich VLDL, thus increasing the plasma triglyceride concentration. Cholesterol ester transfer protein (CETP) transfers cholesterol from HDL to VLDL, exchanging it for triglycerides. Therefore, the HDL cholesterol falls. The increased VLDL also reduces the ability to remove postprandial newly absorbed chylomicrons. In Syndrome X, VLDL, chylomicrons and their metabolic remnants (chylomicron and VLDL remnants) are removed more slowly from the plasma by virtue of their increased concentrations, resulting in increased postprandial lipemia. In addition, there is a shift in the LDL particle diameter to smaller and denser LDL particles.

3. Uric acid metabolism: There is a tendency to increased serum uric acid concentration. There is a decrease in the ability of the kidney to excrete uric acid, so renal uric acid clearance is decreased.

4. Kidney manifestation: There is an increased salt retention. It appears that half the patients with hypertension are insulin resistant. From population based studies, the best predictor of hypertension developing has been hyperinsulinemia as a surrogate measure of insulin resistance.

5. Hemodynamic manifestations: There is evidence that the sympathetic nervous system activity is increased in insulin resistant individuals. This is another example of other tissues reacting to the hyperinsulinemia.

6. Fibrinolytic changes: There is an increase in PAI-1, with a resultant decrease in fibrinolysis. The increase in fibrinogen tends to increase coagulation.

All of these manifestations can have some role in the development of coronary heart disease. Even though some of these manifestations may not be easily measured in the clinical laboratory, a good thorough evaluation would include:

• A **family history** of type 2 diabetes, CHD, or hypertension increases the risk for Syndrome X.

• **Fasting triglyceride level** above 1.9 mmol/L, certainly above 2.6 mmol/L, is a very good surrogate marker of the increase in postprandial lipemia, the appearance of small dense LDL, and the increase in PAI-1 levels.

• **HDL cholesterol** less than 1.0 mmol/L is also a good indicator of insulin resistance.

• Fifty percent of individuals with **hypertension** have insulin resistance.

• **Fasting glucose above 5.5 mmol/L** indicates a person is at risk of insulin resistance. We have shown the higher the glucose within the normal glucose range, the greater the insulin resistance. A two hour glucose concentration post glucose load of greater than 7.8 and less than 11.1 mmol/L, may not merit the diagnosis of type 2 diabetes, but would suggest insulin resistance.

You get a very shrewd idea from these very simple measurements of the presence of insulin
resistance and the risk for CHD.

**Q. What is the relationship between Syndrome X and CHD?**

**A.** Only one study has shown that in people followed prospectively, insulin resistance increases the risk of CVD. There are multiple studies showing insulin level, as a predictor or surrogate measure of insulin resistance, predicts CHD. We also know that a low HDL is a powerful predictor of CHD. There is more and more evidence that small dense LDL particles and increased remnant lipoprotein concentrations due to the increased postprandial lipemia are linked to CHD. The relationship is not Syndrome X leading to CHD or one factor being responsible for the increased risk, but rather that, taken as a cluster, there is increased prevalence of CHD in people with insulin resistance and the various manifestations.

**Q. By mediating the factors associated with Syndrome X, can we actually improve morbidity and mortality in patients with established CHD?**

**A.** This is a conceptual question now. In the most recent UKPDS study in the UK, lowering glucose did not have very beneficial effects in reducing CHD. In the same study, lowering BP, which is very effective in reducing stroke and congestive heart failure, had no impact on reducing CHD. In all the studies of BP intervention, the effect on reducing stroke is dramatic, but the effect on reducing CHD always lags far behind. There are multiple reasons for why the treatment of type 2 diabetes and hypertension has resulted in less improvement in CHD than expected. It is likely associated with more insulin resistance related factors being present in these individuals other than just high glucose or hypertension. These multiple risk factors have to be addressed if we are going to make any improvement in CHD risk reduction.

**Q. Do we know what actually causes insulin resistance?**

**A.** No, but we do know some interesting things. There is evidence of a widespread variability in insulin mediated glucose disposal by muscle in non-diabetic individuals. Our studies, in 500 such individuals, have shown a ten-fold difference between the most insulin sensitive and the most insulin resistant non-diabetic individual. Some time ago, in collaboration with a group in Phoenix, Arizona, we studied a group of non-diabetic Pima Indians and a group of non-diabetic people of European ancestry living in the San Francisco Bay area. About half of the variability in insulin resistance, comparing these two groups, was due to either differences in maximal aerobic capacity or differences in obesity. These two factors were approximately equally powerful. The other fifty percent was unaccounted for, and likely familial related. To summarize, half of the variability from person to person in terms of the degree of insulin resistance is due to their genes and about half is due to lifestyle variables. Of equal importance, are the differences in degrees of obesity and degrees of fitness. We do not know the molecular genetic defect. Compared to LDL cholesterol, which is more genetically regulated, there is more potential impact of lifestyle change on insulin resistance. There are also enormous ethnic differences. Every ethnic group of non-European ancestry, when matched for variables, is more insulin resistant. The most insulin resistant group studied is South Asian Indians.

**Q. You have underlined in your book that the opposite is not true, that is, insulin resistance does not cause obesity. Could you elaborate?**

**A.** The notion is almost ludicrous. Hyperglycemia and diabetes can be due to either not enough insulin or too much insulin resistance, relative to the degree of insulin secretion. If you have no insulin and a defect in glucose uptake, you develop insulin resistance and you don’t gain weight, you lose weight. If the tissue is resistant to insulin, you can’t utilize your energy normally, and you lose weight. Data supports that higher insulin levels are there to restore normal glucose uptake. Prospective studies have shown that the more insulin resistant a person, as assessed by the surrogate measure of insulin level, the less or the same weight is gained.

**Q.** Once Syndrome X is identified, what are the management strategies we can implement to reduce
risk in our patients?

A. If you are overweight and are insulin resistant, there is no doubt that if you lose weight you will dramatically improve your insulin resistance and the insulin and triglyceride levels will fall. A fifteen pound weight loss will have a dramatic improvement in Syndrome X manifestations, including hypertension. A regular exercise program, 3-4 days/week, for at least 30 minutes, will result in improved insulin sensitivity, triglycerides, and HDL cholesterol. The relative superior effect of weight loss over exercise is that if the 15 lb. weight loss is maintained you maintain the benefit. Whereas, the benefits of exercise are reversed, when exercise is stopped. However, the available information does indicate that the two interventions are equally powerful.

The more controversial question is, if you are not losing weight, what should be the macronutrient content of your diet. The evidence clearly suggests that saturated fat intake should be limited to reduce LDL cholesterol. The problem is, what do you add to the diet to replace the saturated fat, if the person is not gaining weight. Up to now, advice has been to replace the saturated fat with carbohydrate. If a person is insulin sensitive, this advice is acceptable and there are no adverse effects. However, if the person is insulin resistant, increased amounts of insulin are already being secreted throughout the day in response to food intake. A diet with more carbohydrates will worsen the manifestations. It will raise triglycerides, insulin levels and postprandial lipemia, and small dense LDL will appear. Four different approaches have been proposed:

- The Atkins diet suggests, no matter what, you should reduce carbohydrate and increase fat. This will clearly raise LDL cholesterol.

- Replacing the carbohydrate with protein ignores the fact that protein is not absorbed as protein. Protein, in the intestinal tract, converts to amino acid. Amino acids increase insulin secretion. We do not know if they are as potent as carbohydrates in stimulating insulin secretion. This depends on the type of amino acid being released and the type of carbohydrate ingested. It will, no doubt, have an influence on beta cell function.

- Replacing saturated fat with mono- and poly-unsaturated fat will equally benefit LDL cholesterol lowering as compared to replacing saturated fat with carbohydrate. This is confirmed in multiple studies. Mono- and poly-unsaturated fat do not raise insulin levels, so you get the benefit on both LDL cholesterol and Syndrome X.

- It has been postulated that use of low glycemic-index carbohydrates will avoid worsening the manifestations of Syndrome X. If very high fibre food choices are made, the carbohydrate-induced increase in insulin secretion may possibly be mediated. However, when we studied this, by increasing the fibre to the level recommended by the ADA for diabetics, it had almost no effect. In a recent paper, substantial increases in the fibre level (exceeding the ADA recommendation) resulted in improved metabolic characteristics, as compared to a high carbohydrate/low fat diet. No comparison was made between the very high fibre diet vs. a diet low in carbohydrates and high in unsaturated fats.

The simplest and most effective approach is to replace the carbohydrate with poly- and mono-unsaturated fat and restrict saturated fat intake, to achieve both lower LDL cholesterol and improve Syndrome X.

Q. Would you add the goal of reducing waist circumference with weight loss, to improve Syndrome X and its manifestations?

A. No. I am less impressed with any untoward impact of regional obesity. The issue of adipose tissue distribution has been overstated, and is not strongly supported by available data. If you lose weight, you lose it everywhere. I agree that the fad diets are likely to result in fluid loss. I am not particularly focused on losing adipose tissue form site A vs. site B. Caloric deficiency will simply break down adipose tissue. Adipose sites are genetically determined. The only way we can store extra calories in our body is in adipose cells, and where these cells are located is genetically determined. If the
storage locker is in site A. vs. site B, that is where the extra calories are stored. When that storage locker is emptied, weight is lost at the site it was stored.

Q. **Specific diet compositions have been recommended for athletes. Are the consequences of a high protein diet for athletes more psychological than physiological?**

A. There is no question about this. These athletes are uniquely insulin sensitive. What they eat is almost irrelevant. A few years ago, carbohydrate loading was touted. Recommendations then changed to high amino acid diets to improve performance. There is no evidence to support these recommendations.

Q. **There appears to be a dose response relationship for different effects of exercise. Do we know what is the ideal ‘dose’ of physical activity to produce significant impact on Syndrome X?**

A. No. This question is not yet possible to answer. Epidemiological studies have shown that modest exercise improves mortality. However, unequivocal metabolic benefits from exercise will not be achieved from a casual walk a couple of nights a week. Significant, regular, chronic exercise is required to see improvements in insulin action, triglycerides, and HDL cholesterol.

Q. **What is the impact of other lifestyle strategies, like alcohol and smoking?**

A. There is very good evidence that moderate drinkers have lower morbidity rates, probably due to their higher HDL cholesterol. In population based studies, moderate drinkers are found to have lower insulin levels as compared to non-drinkers. Our small-scale studies have shown moderate drinkers to be more insulin sensitive. There have been no intervention studies to show that initiating alcohol consumption in individuals who are insulin resistant with low HDL is beneficial. So it is not reasonable to suggest that non-drinkers should start to drink 1-2 drinks per day. On the other hand, we do not have the evidence to recommend abstaining from alcohol. Smoking is unequivocally bad, including the association with high triglycerides, low HDL cholesterol and insulin resistance.

Q. **Would intervention strategies be any different in patients with documented coronary artery disease?**

A. The only difference might be the amount of exercise that could be safely carried out.

Q. **What comprises the medical management of Syndrome X?**

A. In the presence of Syndrome X and high LDL, the lipid-lowering drugs are useful. In terms of hypertension, some judgment should be used on which medication is used depending on the clinical metabolic profile. In patients with high triglycerides and low HDL cholesterol, lowering triglycerides with fibric acid derivatives will improve outcome.

Q. **Would you have any specific concerns about anti-hypertensive drugs, such as diuretics, that are not favourable to insulin resistance?**

A. Diuretic use, particularly, should be limited. There should never be more than 12.5 mg of hydrochlorothiazide prescribed. As long as low dose thiazides are used, there should not be a problem. People with Syndrome X should not be prescribed the anti-hypertensive dosages of thiazides that have been recommended in the past.

Q. **What are some of the topics that are currently being researched in relation to insulin resistance and Syndrome X?**

A. One of the most interesting questions is why does insulin resistance occasionally become type 2 diabetes. We are studying insulin resistant non-diabetics and intervening with the new insulin sensitizer drugs, which are now only approved for lowering glucose. We are assessing if insulin resistance can be fundamentally improved and CHD risk reduced.
We have shown that individuals who are insulin resistant and hyperinsulinemic have beta cells that act differently. The beta cells of the pancreas are hypersecreting at a given incremental rise in plasma glucose. We know the more insulin resistant the individual, the more hyperactive the beta cell. We are trying to see if the insulin sensitizer drugs, by improving insulin resistance, also return beta cell function to a more normal state. This should give us insight into whether we can prevent the conversion of Syndrome X into type 2 diabetes.

Given the great increase in type 2 diabetes in young adolescents, we also hope to do studies in this population. In addition, we will be studying diet in post menopausal women and in ethnic groups that are more at risk for CHD, and comparing these to groups with lower risk.