

# Syndromes X: A Short History

Gerald M. Reaven, MD

*Division of Cardiovascular Medicine, Stanford University School of Medicine, Stanford, CA*



I feel somewhat presumptuous in attempting to write a short history of Syndrome X, but maybe I can redeem myself if I spend less time on the historical aspects and focus more on some comments as to what Syndrome X is and isn't.

The notion of Syndrome X sprung almost full-blown into my mind in the early Spring of 1988, as I was struggling to prepare my Banting Award address (1). I assumed that I was being honored for the fact that our research group had been among the first to champion the idea that resistance to insulin-mediated glucose disposal was a characteristic of patients with what was then called maturity-onset diabetes, soon metamorphosing into noninsulin-dependent diabetes mellitus, before becoming type 2 diabetes. Irrespective of what it was named, by the time I was preparing my Banting presentation, it was generally agreed that the majority of patients with this clinical syndrome were insulin resistant. However, it had become equally clear that insulin resistance, *per se*, may be a necessary defect in the development of type 2 diabetes, but that frank hyperglycemia only occurred in insulin resistant patients when they were unable to secrete enough insulin to overcome the defect in insulin action.

Surprisingly, at the same time the importance of insulin resistance in the pathogenesis of type 2 diabetes had become common currency, it was also becoming apparent that most insulin resistant patients did not develop type 2 diabetes. Rather, they continued to secrete large amounts of insulin, and the compensatory

hyperinsulinemia was sufficient to prevent frank decompensation of glucose tolerance. Unfortunately, this was hardly a total victory. One of the earliest published efforts of our research group had shown that nondiabetic individuals, clinically stable many months after a myocardial infarction, were somewhat hyperglycemic and hypertriglyceridemic as compared with a matched control group (2). In a subsequent series of studies, we were able to demonstrate that hypertriglyceridemia in most instances was due primarily to increased hepatic secretion of very low density lipoprotein (VLDL)-triglyceride (TG), secondary to insulin resistance/hyperinsulinemia (3). It soon was recognized that hypertriglyceridemia was very often associated with a low high-density lipoprotein (HDL) cholesterol concentration and that both changes were independently associated with insulin resistance/hyperinsulinemia (4). The notion of a relationship between insulin resistance/hyperinsulinemia and high blood pressure began to develop ~15 years ago (5) and has continued to gain momentum. Despite the growing evidence that insulin resistance/hyperinsulinemia played a causal role in a cluster of abnormalities, all of which increased risk of coronary heart disease (CHD), it seemed to me that, despite the obvious importance of these research findings, very little attention was awarded to the importance of insulin resistance and its manifestations as CHD risk factors. What better place to formally introduce the notion of a poorly recognized cluster of abnormalities related to insulin resistance playing a central role in atherogenesis than the annual meeting of the American Diabetes Association?

The X in Syndrome X was used to emphasize the fact that the importance of insulin resistance as a CHD risk was relatively unknown. The notion of a syndrome was to acknowledge that there were several downstream manifestations of insulin resistance and that the number of these present in a given individual would certainly vary; an important issue to be discussed subsequently. Finally, although insulin resistance is most likely the fundamental defect in both type 2 diabetes and Syndrome X, the pathophysiology of the two entities is certainly not the same. Considering them separately seemed to be the first step in beginning to focus on the fact that CHD risk factors in normotensive, nondiabetic individuals includes more than a high LDL cholesterol concentration.

**Table. Abnormalities Associated with Syndrome X.**

1. Glucose Tolerance
  - a) Impaired fasting plasma glucose concentration
  - b) Impaired glucose tolerance
2. Uric Acid Metabolism
  - a) ↑Plasma uric acid concentration
  - b) ↓Renal uric acid concentration
3. Dyslipidemia
  - a) ↑Plasma triglyceride concentration
  - b) ↓HDL cholesterol concentration
  - c) ↑Postprandial lipemia
  - d) ↓LDL particle concentration
4. Hemodynamic
  - a) ↑Renal sodium retention
  - b) ↑Sympathetic nervous system activity
  - c) ↑Blood pressure
5. Procoagulant state
  - a) ↑Plasminogen activator inhibitor-1
  - b) ↑Fibrinogen
6. Reproductive Physiology
  - a) Polycystic ovary syndrome

Syndrome X, as outlined in its original version, suggested that insulin-resistant, nondiabetic individuals would be at increased risk to be somewhat glucose intolerant, dyslipidemic, with a high TG and low HDL cholesterol concentration, and hypertensive (1). Since that time, the number of abnormalities shown to be associated with insulin resistance/compensatory hyperinsulinemia has expanded as shown in the Table. In addition, it has become apparent that insulin resistance/compensatory hyperinsulinemia, and associated abnormalities, represent an important, if not the major, cause of atherogenesis.

Readers who might desire a more complete historical account of the emergence of insulin resistance as a major risk factor for the common diseases of Western civilization can find it in a recently published review (6). However, before closing I believe there are two issues worthy of comment.

Not all overweight individuals are insulin resistant, nor are all insulin resistant individuals overweight. There is no doubt that the heavier an individual, the more insulin resistant. However, only ~25% of the variability in degree of insulin resistance in nondiabetic individuals can be accounted for by differences in degree of obesity. Perhaps the most compelling evidence in support of this point of view comes from the results of the European Group for the Study of Insulin Resistance (7).

Syndrome X should not be defined by the presence of a specific number of related abnormalities. A corollary is that use of statistical

techniques to decide what comprises Syndrome X is likely to do more harm than good. The number of abnormalities associated with insulin resistance/compensatory hyperinsulinemia in any individual will vary directly as a function of the criteria used. For example, since plasma TG concentrations are often defined as abnormal if they exceed 200 mg/dL, an individual with a value of 175 mg/dL would not be considered to have an abnormality of TG metabolism. On the other hand, postprandial lipemia would certainly be accentuated at this plasma TG concentration and LDL particle diameter would be decreased. These latter two changes have been identified as being related to both insulin resistance/compensatory hyperinsulinemia and increasing CHD risk. Yet because these latter two changes are not routinely measured, the individual in this instance, because the plasma TG concentration did not exceed an arbitrary value, would be said not to have Syndrome X.

Syndrome X is not a disease. It cannot be defined by an arbitrary collection of abnormalities. Insulin resistant/hyperinsulinemic individuals are at increased risk to develop any or all of the potential manifestations listed in the Table. How many and in what combination will depend upon a number of other factors beyond the scope of this article.

In summary, within slightly more than a decade it has been well recognized that there are relatively enormous variations in the ability of insulin to stimulate glucose disposal in otherwise healthy individuals. It is now apparent that the combination of insulin resistance, and the compensatory hyperinsulinemia that prevents insulin resistant individuals from developing type 2 diabetes greatly increases the risk of CHD. Indeed, it seems quite likely that the next decade will see Syndrome X replace hypercholesterolemia as the major CHD risk factor.

## References

1. Reaven GM. Role of insulin resistance in human disease. *Diabetes* 1988;37:1595-1607.
2. Reaven G, Calciano A, Cody R, et al. Carbohydrate intolerance and hyperlipemia in patients with myocardial infarction without known diabetes mellitus. *J Clin Endocrinol Metab* 1963;23:1013-1023.
3. Olefsky JM, Farquhar JW, Reaven GM. Reappraisal of the role of insulin in hypertriglyceridemia. *Am J Med* 1974;57:551-560.
4. Laws A, Reaven GM. Evidence for an independent relationship between insulin resistance and fasting plasma HDL-cholesterol, triglyceride and insulin concentrations. *J Intern Med* 1992;231:25-30.
5. Reaven GM, Hoffman BB. A role for insulin in the etiology and course of hypertension? *Lancet* 1987;2:435-437.
6. Reaven GM. Insulin resistance and human disease: a short history. *J Basic Clin Physiol Pharmacol* 1998;9:387-406.
7. Ferrannini E, Natali A, Bell P, et al. Insulin resistance and hypersecretion in obesity. *J Clin Invest* 1997;100:1166-1173.