

## Syndrome X: what's old, what's new, what's etiologic?

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*J Clin Invest.* 1993;92(1):3-3. <https://doi.org/10.1172/JCI116566>.

Editorial

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In this issue of *The Journal* Chen et al. (1) report that individuals with insulin resistance (IR) have small, dense LDL. In discussing their finding, I will trace our increasing awareness of Syndrome X (2), within which most investigators would include IR, hypertriglyceridemia (with low levels of HDL cholesterol), hypertension, and central obesity. I will also discuss the possible etiologies of this common cluster of risk factors for atherosclerotic cardiovascular disease (ASCVD).

*What's old?* In the early 1960's, Albrink and colleagues described a link between ASCVD, diabetes, and plasma triglyceride levels (TG) (3). In 1967, Reaven et al. (4) reported the link between hypertriglyceridemia, increased levels of plasma insulin, and glucose intolerance. A short time later, they showed that IR was a primary defect in both glucose intolerance and non-insulin-dependent diabetes mellitus (5). In the early 1980's, reports from several investigators, including Kissebah et al. (6), provided evidence for a key role of central, intraabdominal obesity. Finally, the association of hypertension with insulin resistance solidified the relationship between the cluster of metabolic abnormalities and ASCVD.

*What's new?* Where does small dense LDL fit in this picture? Small, dense, cholesteryl ester depleted LDL particles predominate in individuals with higher VLDL and intermediate density lipoproteins, and lower HDL levels. Cholesteryl ester transport protein (7) is a likely link between abnormalities in lipoprotein concentration and composition. Thus, increased levels of the TG-rich precursors of LDL can stimulate increased exchange of TG for both HDL and LDL cholesteryl esters. So it was a good bet that, if IR was closely associated with hypertriglyceridemia, it would also be associated with small dense LDL. In fact, Reaven et al. (1) found that TG concentration was the best predictor of LDL size after multiple regression analyses. This does not mean that the finding is trivial, however. First, there may be other origins of small dense LDL, such as selective increases in the secretion of targeted apoB-lipoprotein precursors: Increased secretion of apoB-containing lipoproteins has been demonstrated in patients with Syndrome X. More important, the finding of a predominance of small, dense LDL potentially provides a new link between Syndrome X and ASCVD: Small, dense LDL more readily undergo oxidative modification, an important step in the development of the fatty streak.

*What's etiologic?* While the addition of small, dense LDL offers a more direct link between Syndrome X and ASCVD, it does not, unfortunately, provide new insight as to the etiology of this complex clustering of phenotypes. Although Krauss and

his co-workers have found a link between small, dense LDL and specific chromosomal loci, it is very unlikely that a shift in mean LDL diameter is the central abnormality in this syndrome. The two favored etiologic candidates are IR and central obesity. IR as the primary defect would clearly increase an individual's predisposition for non-insulin-dependent diabetes mellitus. It could also result in abnormalities leading to increased plasma fatty acid flux and increased secretion of apoB-containing lipoproteins by the liver (8). On the other hand, primary defects in lipogenesis and/or lipolysis in the intraabdominal fat depot could provide increased fatty acids to both drive secretion of apoB-lipoproteins and compete for insulin-mediated glucose metabolism (9). In either case, IR-driven hyperinsulinemia could set the stage for hypertension.

Can a single defect result in the entire cluster of abnormalities? Although measures of IR appear to be related to glucose, triglyceride, and blood pressure levels in a continuous manner, available data indicate that other genetic predispositions are needed for the appearance of the diseases of Syndrome X; diabetes, dyslipidemia, and hypertension. On the other hand, the risk of ASCVD increases continuously as glucose and blood pressure levels rise, and as HDL levels fall, even in the absence of defined disease states. Thus, we must remember that while patients with Syndrome X may present with only one of its associated diseases, they will very likely have other metabolic abnormalities that, while not meeting the criteria for diseases, will increase their risk for developing ASCVD.

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J. Clin. Invest.

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0021-9738/93/07/0003/01 \$2.00

Volume 92, July 1993, 3