Insulin Resistance Has Independent Role in Atherogenesis

Written by Lori Alexander

In conditions with insulin resistance, it is well established that systemic abnormalities, such as dyslipidemia and hypertension, can effect cells in the vascular wall and cause atherosclerosis. Emerging research suggests that insulin resistance within vascular endothelial cells can lead directly to atherosclerosis independently of systemic factors. This effect is large and may be a major determinant of atherosclerosis in metabolic syndrome or type 2 diabetes, said Christian Rask-Madsen, MD, PhD, Joslin Diabetes Center and Harvard Medical School, Boston, Massachusetts, USA.

Dr. Rask-Madsen explained that evidence for the presence of endothelial insulin resistance is based on studies of several animal models of obesity-associated insulin resistance that have shown impaired insulin signaling in vascular tissue and in primary endothelial cells. Impaired insulin signaling has also been found in primary endothelial cells that have been isolated from human donors with certain polymorphisms of genes that are involved in insulin signaling, such IRS1, TRIB3, and ENPP1. In addition, insulin can augment resting blood flow or blood flow that is stimulated by acetylcholine or other agonists, and these effects of insulin are, at least in part, mediated by the endothelium-derived factor nitric oxide.

Dr. Rask-Madsen said that studies have indicated that the mechanisms that cause insulin resitance in endothelial cells may be quite different from mechanisms that cause systemic effects. However, data suggest that endothelial insulin resistance is reversible. In a study of patients with poor glycemic control and a mean HbA1C of 10%, intensive control of blood glucose lowered the HbA1C to 7.5% and improved insulin-stimulated endothelial vasodilator function [Rask-Madsen C et al. *Diabetes* 2001].

Several endothelial cell functions are stimulated by insulin, and the effects of insulin can both prevent and promote atherosclerosis. Most of the evidence of these effects has come from *in vitro* studies, so it is not clear whether insulin resistance in endothelial cells accelerates or delays atherosclerosis.

Dr. Rask-Madsen described his recent research, which was designed to answer this question [Rask-Madsen C et al. *Cell Metab* 2010]. Using a special mouse model (endothelial insulin receptor and ApoE knockout; EIRAKO), he and his colleagues were able to achieve insulin resistance that was isolated to endothelial cells, with no changes in systemic factors, such as glucose metabolism, lipid levels, and blood pressure. Compared with littermate controls, EIRAKO mice had atherosclerotic lesions that were up to 3-fold larger, with more complex plaque composition.

In vivo microsopy showed that leukocyte rolling and adhesion were increased by up to 4-fold in the EIRAKO mice. This finding is important, said Dr. Rask-Madsen, because the difference occurred despite similarities in systemic factors in the EIRAKO and control mice. Because leukocyte rolling and adhesion occur early in atherogenesis, this physiological abnormality is a clear target for the prevention of atherosclerosis, he added. The increased leukocyte adhesion was found to be due to an increase in VCAM-1 in primary endothelial cells, and injection of VCAM-1 blocking antibody decreased leukocyte adhesion to below control levels.

The findings of the research are important because insulin treatment or insulin-sensitizing therapy may prevent atherosclerosis through effects directly on vascular endothelium. He added that the efficient prevention of cardiovascular disease through insulin-sensitizing therapy may require improvements of endothelial insulin resistance.

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