Study finds excess insulin levels an unlikely cause of atherosclerosis

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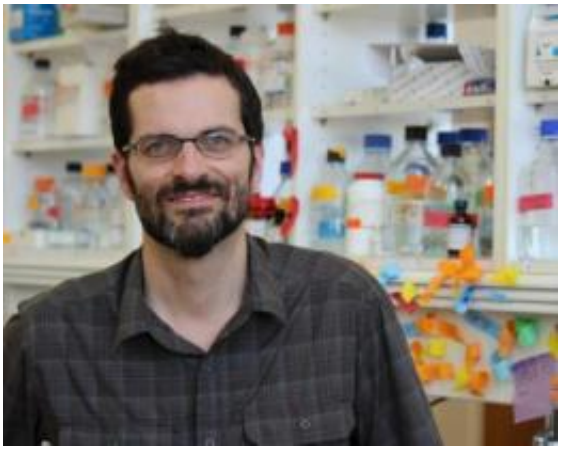

Christian Rask-Madsen, M.D, Ph.D. is a research associate at Joslin's Dianne Nunnally Hoppes Laboratory for Diabetes Complications at the Joslin Diabetes Center Credit: Joslin Communications Office

A number of studies have shown that excess insulin circulating in the bloodstream is a major independent risk factor for cardiovascular disease. However, a new study from Joslin Diabetes Center finds that this condition, called hyperinsulinemia, is itself not a cause of atherosclerosis.

In humans, insulin resistance, a condition in which insulin becomes less effective at lowering blood sugar levels, coexists with hyperinsulinemia. Both are associated with atherosclerosis, the buildup of cholesterol in blood vessels that causes coronary artery disease, heart attack, and

stroke. In this condition, vascular cells could become dysfunctional because of hyperinsulinemia or because vascular cells themselves are insulin resistant, which is caused by increased insulin production from pancreatic beta cells as a compensatory mechanism to overcome insulin resistance.

Scientists have known for some time that insulin resistance and hyperinsulinemia cause increased lipids in the circulation, which indirectly leads to atherosclerosis. However, the Joslin study, published in the May issue of the journal *Arteriosclerosis, Thrombosis, and Vascular Biology*, shows that, without other factors such as high blood pressure and high cholesterol, hyperinsulinemia alone does not cause atherosclerosis.

"For years, scientists have suspected that high levels of insulin could affect vascular cells negatively," says lead author Christian Rask-Madsen, MD, PhD, a research associate at Joslin's Dianne Nunnally Hoppes Laboratory for Diabetes Complications. "We know that people with type 2 diabetes and insulin resistance are susceptible to atherosclerosis, but our study shows that excess insulin alone does not promote this complication."

To study the effects of hyperinsulinemia on atherosclerosis, Rask-Madsen and his colleagues created mice with fewer insulin receptors in every tissue of the body and compared them to mice with intact insulin receptors. Insulin receptors make cells responsive to insulin, a hormone that circulates in the bloodstream. Both sets of mice were genetically modified to have high cholesterol, but were similar in terms of body weight, glucose metabolism, and lipid and blood pressure levels.

Reducing the insulin receptors from one set of mice did not significantly impair their glucose metabolism, says Rask-Madsen-certainly not enough to make the animals overtly insulin resistant-but it did increase the

amount of circulating insulin by reducing its removal from the blood. This model allowed the researchers to study the effects of hyperinsulinemia without the confounding effects of insulin resistance.

The new findings build on a 2010 study conducted by Rask-Madsen, which found that insulin resistance only in endothelial cells is sufficient to increase susceptibility to atherosclerosis. George King, MD, Joslin's chief scientific officer, is the senior author of both studies.

Taken together, Rask-Madsen says, the findings of the two studies suggest that "when we look at new ways to prevent atherosclerosis, we should focus on improving insulin signaling in vascular cells rather than blocking the action of insulin in these cells."

Provided by Joslin Diabetes Center