Unraveling Reaven’s Syndrome X: Serum Insulin-Like Growth Factor-I and Cardiovascular Disease

To the Editor:

Juul et al.1 describe the interesting observation that low serum insulin-like growth factor-I (IGF-I) and high IGF-binding protein-3 (IGFBP-3) are associated with an increased occurrence of cardiovascular disease.

In line with their observation, we recently demonstrated that low plasma IGF-I levels were associated with postprandial dyslipidemia and insulin resistance. Postprandial dyslipidemia is an atherogenic risk factor, and this postprandial period is dominated by triglyceride-rich particles (TRPs) and high atherogenic TRP remnants, such as the remnant-like particle (RLP). Fasting and postprandial plasma RLP cholesterol (RLP-C) levels in hypercholesterolemic familial hypercholesterolemia have been reported by our group to be an additional factor in the atherogenic lipoprotein.2,3 The postprandial accumulation of RLP-C in adult growth hormone (GH)-deficient subjects is inversely associated with pretreatment plasma IGF-I levels; consequently, the lower the serum IGF-I level, the higher the postprandial RLP-C load.4 It is established that GH directly affects the expression of the hepatic low-density lipoprotein receptors and of key enzymes implicated in bile acid metabolism with effects on the intracellular cholesterol homeostasis in the liver; such homeostasis is linked to metabolism of TRPs. Consequently, the question arises whether the pituitary GH secretion capacity in the participants of the report by Juul et al.1 may be impaired.

Additionally, knowledge about free IGF-I levels, and thus the biological active form, in the population studied by Juul et al.1 is of major importance to more precisely understand their reported positive associations. Most circulating IGF-I is bound to IGFBP-3. Consequently, proteolysis of IGFBP-3 modulates the IGF bioavailability. In insulin-resistant subjects, the proteolysis of IGFBP-3 is increased, and this regulation mechanism for free exchangeable IGF-I in circulation keeps the IGF/intact IGFBP-3 ratio constant. A low total IGF level in insulin resistance may therefore have no biological consequences, and moreover, is influenced by glucose homeostasis.5 In line with these results, more details about glucose homeostasis from the participants in the report by Juul et al.1 and a calculation of a IGF-1/IGFBP-3 ratio in relation to the occurrence of ischemic heart disease will be of additional interest.

The association that is found by Juul et al.1 is an important observation that gives another opportunity to find new pathways that may unravel the anchor points of Reaven’s metabolic syndrome X.

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To the Editor:

Juul et al.2 have recently documented that low circulating insulin-like growth factor-I (IGF-I) and high IGF binding protein-3 (IGFBP-3) levels significantly increase the risk of ischemic heart disease. The prognostic impact of IGF-I and IGFBP-3 remained significant after correction for potential confounding factors, but the authors made no specific comments on any possible association between serum IGF-I and cholesterol. We have recently observed an increase of IGF-I after lipid-lowering therapy,2 which suggests that some relation between serum lipids and IGF-I might exist.

We have therefore compared circulating IGF-I and IGFBP-3 levels in 27 otherwise healthy subjects with severe isolated hypercholesterolemia (total cholesterol 8.59±0.72 mmol/L, age 52±11 years [mean±SD]) and in 31 age- and sex-matched healthy controls (total cholesterol 5.63±0.58 mmol/L). IGF-I and IGFBP-3 levels were determined by radioimmunoassay (Immunotech); for each subject, we also calculated IGF-I/IGFBP-3 ratio, an indirect indicator of biologically active free IGF-I. These values are expressed as medians [25th, 75th percentiles]; inter-group comparisons were performed by Mann-Whitney U test. Hypercholesterolemic subjects had lower IGF-I levels (median: 181 [25th, 75th percentile: 132, 223] versus 240 [187, 286] µg/L, P=0.001), higher IGFBP-3 levels (4.8 [4.2, 5.3] versus 3.6 [3.3, 4.0] µg/mL, P<10⁻³), and a lower IGF-I/IGFBP-3 ratio (35.2 [31.1, 42.9] versus 62.4 [50.7, 74.5], P<10⁻³) than controls. Together with our earlier observations,2 these data suggest a possible link between circulating IGF-I and lipids.

The intriguing work by Juul et al.1 documents that the association of IGF-I and its binding proteins with atherosclerosis is clinically relevant. Our results further extend their observations, suggesting that serum cholesterol, a risk factor of atherosclerosis, may be directly involved in this relationship. Therefore, some association between IGF-I and lipids might also exist in the study of Juul et al.,1 and perhaps the authors have some additional data to further clarify this issue.

To the Editor:

We read with satisfaction the article by Juul et al, 1 which showed in a nested case-control study that individuals with low circulating insulin-like growth factor (IGF)-I and high IGF-binding protein (BP)-3 levels have a significantly increased risk of myocardial infarction (MI) and cardiovascular death during a 15-year follow-up, independent of traditional risk factors. Although the accompanying editorial 2 found the results “contrary to the beliefs of many,” increasing clinical and experimental evidence not quoted by Juul et al supports the contention that reduced IGF-I represents a new risk factor for ischemic heart disease, closely linked to glucose intolerance and type 2 diabetes.

Indeed, we recently found markedly reduced serum IGF-I levels in patients with acute MI compared with healthy controls, preceding the rise in markers of myocardial necrosis; notably, among patients with MI, IGF-I concentrations were significantly lower in those with adverse events compared with those with an eventful course. 3 Furthermore, the absence of a 192-bp allele in the promoter of the IGF-I gene on chromosome 12 has been associated with reduced circulating IGF-I, an increased risk for type 2 diabetes and MI, and an especially high risk of MI (odds ratio 3.4, 95% confidence interval 1.1 to 11.3) among patients with MI, IGF-I concentrations were significantly reduced IGF-I represents a new risk factor for ischemic heart disease, closely linked to glucose intolerance and type 2 diabetes.

We found that the cardiovascular risk attributed to IGF-I was significantly diminished when we adjusted for lipids. Although IGF-I remained a significant risk factor after adjustment for lipids, part of the association between IGF-I and risk of cardiovascular disease may be accounted for by lipids. We have no information on the pulsatile 24-hour GH secretion in our subjects, but others have found that GH, and not IGF-I, was significantly inversely associated with cholesterol and triglyceride levels in healthy subjects. 3 Thus, we cannot exclude the possibility that IGF-I serves as a proxy for the pulsatile GH secretion. On the other hand, systemic IGF-I treatment in patients with type 1 diabetes results in a lowering of the GH secretion and an increased insulin sensitivity concomitant with a lowering of fasting triglyceride and very low-density lipoprotein-triglyceride concentrations.

Böger and coworkers previously demonstrated that the GH-induced increase in IGF-I was associated with increased urinary excretion of markers of nitric oxide (NO) production (cGMP) in GH deficient adults. Thus, IGF-I may be involved in NO-mediated vasodilation. Another study found that IGF-I correlated positively with blood pressure-corrected aortic distensibility in healthy normotensive adults, 4 and several authors have shown that intravenous infusion of IGF-I in healthy controls increased forearm blood flow, which was blocked by an inhibitor of nitric oxide synthase. Thus, IGF-I may stimulate endothelial NO formation, thereby decreasing peripheral arterial resistance which could also explain, at least in part, our findings of an association between low IGF-I and increased risk of cardiovascular disease.

Insulin resistance is likely to be a major player in the association between IGF-I and cardiovascular risk, as pointed out by Twickler et al in their comment. Clearly, IGF-I improves insulin resistance, and low IGF-I was in fact shown to predict the occurrence of abnormal glucose tolerance testing in a prospective follow-up study of 615 healthy subjects.

Much controversy exists regarding IGF-I levels in patients with heart disease. The strength of our study is the fact that IGF-I was determined many years before signs or symptoms of cardiovascular disease were evident. Clearly, the recent study by Vaessen et al, 5 in which genetic polymorphisms in the promoter region of the IGF-I gene were studied and found to be associated with risk of myocardial infarction, are in strong support of our findings.

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