Low Serum Insulin-Like Growth Factor I Is Associated With Increased Risk of Ischemic Heart Disease

To the Editor:

In a recent interesting paper by Juul et al.¹ and an accompanying editorial by Frystyk et al.,² an association between low insulin-like growth factor I (IGF-I) serum levels and the incidence of ischemic heart disease was reported. The inverse nature of this relationship was unexpected by these authors, and a number of possible mechanisms were discussed.

However, in addition to these authors’ hypotheses about the molecular mechanisms behind this finding, one mechanism that may contribute to the reported role of IGF-I in coronary heart disease was not mentioned: There is experimental evidence that endothelial cells possess high-affinity binding sites for IGF-I, and that the vasodilator effect of IGF-I is abrogated by the NO synthase inhibitor N⁰-monomethyl-L-arginine (L-NMMA).³ These data suggest that IGF-I induces NO-dependent vasodilation. In humans, IGF-I induces endothelium-dependent vasodilation as well, which can also be blocked by co-infusion of L-NMMA.⁴ Furthermore, we found that the increase in serum IGF-I induced by growth hormone supplementation results in elevated urinary excretion of nitrite/nitrate and cyclic GMP, markers of systemic NO production, in adult patients with acquired growth hormone-deficiency⁵ and in patients with cardiomyopathy. In parallel, total peripheral resistance was reduced in both studies, indicating that peripheral vasodilation occurred.

Thus, there is evidence that NO may mediate the cardiovascular effects of IGF-I. Administration of IGF-I has an immediate positive effect on NO formation by endothelial cells. This NO release, given the well-known antiproliferative and antiatherogenic effects of NO, may antagonize many of the proproliferative effects of IGF-I in the cardiovascular system. Reduced endothelial NO elaboration caused by reduced stimulation of endothelial cells by IGF-I may therefore be responsible for many of the detrimental cardiovascular changes associated with low IGF-I levels and may help to explain the inverse relationship between low IGF-I and an increased incidence of coronary heart disease.

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Response

We find Dr Böger’s hypothesis well founded and attractive. Endothelial cells do indeed have insulin-like growth factor I (IGF-I) receptors,¹ and these cells come into direct contact with circulating IGF-I and its binding proteins. This circulating IGF-I system is what was measured in the interesting work by Juul et al.²

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