Increased Proinsulin Concentrations and Excess Risk of Coronary Heart Disease in Patients With Diabetes and Prediabetes

To the Editor:

The evidence relating concentrations of proinsulin to the risk of coronary heart disease is summarized by Haffner and Hanley.1 They point out that few prospective studies have been performed. We have recently published an investigation on the relationship between concentrations of proinsulin-like molecules and incidents of coronary heart disease in 1181 nondiabetic men aged 50 to 64 years and investigated in the Caerphilly study2 in which there were 127 fatal and nonfatal coronary heart disease events during the 10 to 14 years of follow-up. Insulin, intact proinsulin, and des 31, 32 proinsulin were measured with specific antibodies.

In logistic regression analysis for incident coronary heart disease controlling for age and body mass index, both des 31, 32 proinsulin (standardized odds ratio [SOR] 1.38, 95% confidence intervals [CI] 1.02, 1.85; P=0.034) and sum of proinsulin-like molecules (SOR 1.54, 95% CI 1.07, 2.20; P=0.019) were more strongly related to disease than concentrations of insulin (SOR 1.30, 95% CI 0.91, 1.85; P=0.15). In a joint model, des 31, 31 proinsulin retained significance (SOR 1.41, 95% CI 1.00 to 1.99; P=0.05) at the expense of insulin (SOR 0.93, 95% CI 0.62, 1.39; P=0.72). Thus, des 31, 32 proinsulin provides a stronger prediction of incident coronary heart disease than does insulin, despite the fact it comprises only some 10% of the total molecular concentration.

To explore possible mechanisms, we adjusted in further models for several risk factors associated with insulin resistance. The odds ratios were virtually unaffected by inclusion of smoking, blood pressure, or low-density lipoprotein cholesterol, but adding triglyceride and high-density lipoprotein cholesterol to the models reduced the standardized odds ratios by ~50%. Additional adjustment for plasminogen activator inhibitor-1 further reduced the standardized odds ratios by around ~50%. Similar effects of such adjustments were found either in models with insulin and proinsulin-like molecules separately, or in combined models. Further addition of recalled birth weight to these models had little effect on the odd ratios.

Our findings suggest relationships of concentrations of proinsulin-like molecules with incident coronary heart disease independent of obesity and of concentrations of insulin (and thus insulin resistance). These relationships appear in part independent of both dyslipidemia and abnormalities of fibrinolysis associated with the metabolic syndrome. These findings suggest one of two possibilities: (1) that proinsulin-like molecules have actions, either through a proinsulin receptor3 or through other biological mechanisms, that play some role in atherothrombosis; or (2) that higher concentrations of proinsulin-like molecules reflect another unmeasured common antecedent such as concentrations of proinflammatory cytokines.4

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