Do Increased Proinsulin Concentrations Explain the Excess Risk of Coronary Heart Disease in Diabetic and Prediabetic Subjects?

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Type 2 diabetes is associated with a marked increase in the risk of coronary heart disease (CHD). In addition, small increases in glucose concentrations in the non-diabetic range also may be associated with an increased risk of CHD (see the Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Europe [DECODE] study). However, the increase in CHD in diabetic subjects may not be entirely due to increases in glucose levels per se, because in many studies, including the United Kingdom Prospective Diabetes Study (UKPDS), although glucose levels were significantly related to CHD, the magnitude of the association is only modest. One explanation for the increased risk of CHD in diabetics may be the insulin resistance syndrome. A related possibility may be the atherogenicity of the prediabetic state. Indeed, insulin resistance, rather than decreased insulin secretion, seems to be most responsible for the increased cardiovascular risk factors in the prediabetic state (ie, increased triglyceride and blood pressure and decreased high-density lipoprotein cholesterol [HDL-C] even before the onset of diabetes). In some studies, insulin concentrations (as a surrogate for insulin resistance) have been strongly related to CHD; however, in other studies that include meta-analysis, insulin concentrations have been only modestly associated with CHD.


Until recently, most insulin immunoassays cross-reacted with proinsulin. Proinsulin is a precursor of insulin that is enzymatically cleaved to form insulin. Several studies have suggested that proinsulin concentrations may be more strongly related to cardiovascular risk factors (especially increased blood pressure and higher triglyceride levels) than are insulin concentrations. Proinsulin levels increase in subjects as glucose tolerance deteriorates from normal glucose tolerance to impaired glucose tolerance to type 2 diabetes. The increase in proinsulin levels with worsening glucose tolerance is greater than the increase in insulin concentrations, suggesting a worsening defect in proinsulin processing with worsening glucose tolerance. Additionally, proinsulin has been shown to increase plasminogen activator inhibitor-1 (PAI-1) in vitro. Adjustment for PAI-1 levels markedly attenuated the association between proinsulin and carotid wall thickness in the Insulin Resistance Atherosclerosis Study (IRAS), suggesting a role for PAI-1 in mediating this association.

Another possibility for the association between proinsulin and intimal medial wall thickness is automatic dysfunction. Increased proinsulin levels have been associated with the sympathovagal balance of the automatic nervous function both in patients with non–insulin-dependent diabetes mellitus and in control subjects. In spite of the possible associations of proinsulin with cardiovascular risk factors, there are a number of puzzling features. Proinsulin is present in low concentrations except in diabetic subjects. Furthermore, the activity of proinsulin, either in vitro or in vivo, is only about 10% of the biological activity of insulin, so low concentrations of proinsulin are unlikely to have a significant biological, insulin-like effect.

In some studies, proinsulin concentrations also are related to atherosclerosis and cardiovascular disease. In the Insulin Resistance Atherosclerosis Study (IRAS), proinsulin concentrations in non-diabetic subjects were found to be more strongly related to carotid wall thickness than were insulin concentrations. In a small study of Japanese Americans, proinsulin concentrations were not related to the prevalence of CHD. Prospective studies, the relationship of proinsulin to cardiovascular disease has been variable. Yudkin et al found a significant relationship in a cross-sectional but not prospective study from the United Kingdom. Conversely, Lindahl found that high proinsulin concentrations in Swedish subjects predicted acute myocardial infarction and stroke.

The report by Oh et al that appeared in the March 19, 2002, issue of Circulation (Circulation. 2002;105:1311–1316) is an important additional contribution. The Rancho Bernardo study is well done and relatively large, and it also used a specific insulin assay that did not recognize proinsulin. However, the authors did not adjust for glucose tolerance in their multivariate modeling; although glucose tolerance was not significantly different between cases and controls, given the very strong relationship between proinsulin and glucose concentrations, the necessity to adjust for small differences in glucose levels may still be critical.

The study by Oh et al also suggests that the measurement of proinsulin may be an important addition to the prediction of cardiovascular risk for research projects. These results...
need to be confirmed, as the authors correctly state, in additional prospective studies. Given this interesting data, should proinsulin concentrations be measured in clinical practice for prediction of cardiovascular disease? At the present time, proinsulin levels should not be measured because of a lack of standardization. The American Diabetes Association has suggested a significant lack of standardization even for insulin concentrations17 that are more widely used for research and, in some cases, clinical practice. Of interest was the variability in insulin assays that could not be explained by different degrees of cross-reactivity with proinsulin. Clearly, standardization for insulin and proinsulin is necessary before these measures can be clinically useful.

Another issue is whether higher proinsulin concentrations may actually reflect insulin resistance. A number of studies have suggested that proinsulin concentrations are strongly related to insulin resistance.18 To use proinsulin as a possible measure of insulin secretion, it is necessary to calculate proinsulin-to-insulin ratios or, preferably, to adjust the level of proinsulin for the ambient insulin level in multivariate models.

Proinsulin has been shown to be a strong predictor of type 2 diabetes.19 In fact, it is possible that one reason why proinsulin may predict cardiovascular disease in prospective studies is that proinsulin is an excellent predictor of diabetes, and the increased risk of proinsulin for cardiovascular disease might be due entirely to more subjects becoming diabetic in the interval. This criticism cannot, of course, relate to the present cross-sectional study.16

One possible way to take account of the proinsulin levels may be to consider the metabolic syndrome as a risk factor. Proinsulin concentrations are increased in the metabolic syndrome.9 The National Cholesterol Education Panel Adult Treatment Panel III (NCEP ATP III)20 recently has suggested a simple definition of the metabolic syndrome, which includes upper body obesity, high triglyceride levels, low HLD-C, hypertension, and impaired fasting glucose. Individuals who have 3 or more components are defined as having the metabolic syndrome. It is likely that subjects with the metabolic syndrome have proinsulin levels in the upper 20% of the general population. Until the measurement of circulating proinsulin levels becomes standardized, the metabolic syndrome may provide an acceptable surrogate for elevated proinsulin levels in clinical practice.

References


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