Proinsulin and Insulin Concentrations in Relation to Carotid Wall Thickness

Insulin Resistance Atherosclerosis Study

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Background and Purpose—Insulin resistance and hyperinsulinemia have been associated with atherosclerosis. Recent attention has focused on the possible role of proinsulin because most radioimmunoassays for insulin cross-react with proinsulin. Therefore, it is not known which of the two, insulin per se or proinsulin, is more strongly related to atherosclerosis.

Methods—We examined the relation between fasting proinsulin, fasting split proinsulin, fasting and 2-hour insulin (after oral glucose load), and intima-media wall thickness (IMT) in the common carotid artery (CCA) and internal carotid artery (ICA) in 985 nondiabetic subjects from the Insulin Resistance Atherosclerosis Study, a multiethnic study of insulin resistance and atherosclerosis.

Results—In the overall population, a weak but significant relation between proinsulin and CCA IMT was observed ($r=0.07, P=0.029$). However, the relation between proinsulin and IMT was stronger in Hispanics and non-Hispanic whites than in African Americans. In non-Hispanic whites and Hispanics, significant correlations between CCA and proinsulin ($r=0.087$) and between ICA and proinsulin ($r=0.101$), split proinsulin ($r=0.092$), and fasting insulin ($r=0.087$) were observed. The significant correlations became more attenuated (and nonsignificant) after adjustment for cardiovascular risk factors, especially plasminogen activator inhibitor-1 (PAI-1).

Conclusions—The association between proinsulin and IMT, while weak, appears to be stronger than the association between insulin and IMT. Adjustment for PAI-1 markedly attenuated the association between proinsulin and IMT, suggesting a possible mediating role for PAI-1 in this association. It is possible that proinsulin may represent a marker of atherosclerosis rather than a causal factor for atherosclerosis. Studies of the insulin resistance syndrome and atherosclerosis that use insulin as a surrogate for insulin resistance should consider the use of specific insulin assays as well as determination of proinsulin concentrations. (Stroke. 1998;29:1498-1503.)

Key Words: atherosclerosis ■ insulin ■ plasminogen activator inhibitor-1 ■ proinsulin

Insulin concentrations have been related to the incidence of cardiovascular disease in many1–4 but not all studies.5–7 Fasting insulin concentrations were also related to atherosclerosis in the carotid artery in the large Atherosclerosis Risk in Communities Study.8 In smaller Finnish9 and American10 studies, insulin concentrations were not related to atherosclerosis.

Insulin concentration has been considered to be fairly well correlated with insulin resistance ($r=-0.60$) in nondiabetic subjects.11,12 Although no studies have examined insulin resistance in relation to the incidence of cardiovascular disease, a number of studies have shown that subjects with atherosclerosis are more insulin resistant.13–16 Insulin concentrations have been used as a surrogate for insulin resistance in studying the association of insulin with atherosclerosis, since the use of direct methods to assess insulin sensitivity, such as the hyperinsulinemic euglycemic clamp or the frequently sampled intravenous glucose tolerance (FSIGT) test, are expensive and time-consuming and have only limited patient acceptance. One potential problem with the use of insulin concentrations as a surrogate for insulin resistance is that most commercial assays for insulin cross-react with proinsu-
lin. Proinsulin is increased relative to insulin in subjects with type 2 diabetes in all studies\(^\text{12-23}\) and elevated in subjects with impaired glucose tolerance in most\(^\text{23,24}\) but not all\(^\text{20}\) studies. Increased proinsulin has been more strongly correlated with cardiovascular risk factors than insulin in both diabetic\(^\text{25,26}\) and nondiabetic\(^\text{27-29}\) subjects. Relatively few data are available on the relation of proinsulin to cardiovascular disease or atherosclerosis. Kahn et al\(^\text{30}\) found a relation of insulin (but not proinsulin) to prevalent coronary heart disease (CHD) in 170 Japanese Americans. In contrast, Båvenholm et al\(^\text{31}\) found a significant relation between both insulin and proinsulin with CHD in 62 men; these associations were no longer significant after adjustment for body mass index (BMI). Yudkin et al\(^\text{32}\) found modest (but significant) relations between both insulin and proinsulin and prevalent CHD; these results were no longer significant after adjustment for BMI. In the longitudinal study,\(^\text{33}\) no significant relation between insulin or proinsulin and CHD was observed. In small studies of proinsulin with atherosclerosis, no significant associations were observed.\(^\text{3,10}\)

In this report, we examine the association between insulin, proinsulin, and atherosclerosis as determined by B-mode imaging of the carotid artery intima-media thickness (IMT) in 985 nondiabetic subjects in a large multicenter, multiethnic study, the Insulin Resistance Atherosclerosis Study (IRAS).\(^\text{34}\) This imaging technique has been shown to reflect histopathologically verified atherosclerosis\(^\text{35,36}\) and therefore has been widely used as a noninvasive method for assessing atherosclerosis.\(^\text{36,37}\) Because proinsulin levels have been associated with cardiovascular risk factors, we also assess whether relations between proinsulin and atherosclerosis may be attributed to cardiovascular risk factors. We have previously reported the relationship of insulin sensitivity to atherosclerosis in the IRAS.\(^\text{38}\)

**Subjects and Methods**

A detailed description of the design and methods of the IRAS has been published.\(^\text{39}\) In brief, this study was conducted at 4 clinical centers. Clinical centers in Oakland and Los Angeles, Calif, studied non-Hispanic whites and African Americans recruited from Kaiser Permanente, a nonprofit health maintenance organization. Clinical centers in San Antonio, Tex, and San Luis Valley, Colo, studied non-Hispanic whites and Hispanics recruited from 2 ongoing population-based studies (San Antonio Heart Study\(^\text{40}\) and San Luis Valley Diabetes Study\(^\text{41}\)). Diabetic subjects taking insulin were not eligible for the IRAS. Of all eligible subjects, 48% contacted the 2-day IRAS examination. Diabetic subjects with a fasting glucose level \(\geq 300 \text{ mg/dL} \ (\geq 16.7 \text{ mmol/L})\) were excluded. The fasting glucose levels of Hispanic, African American, and non-Hispanic white diabetic and nondiabetic subjects in the IRAS were similar to those of their counterparts in the NHANES survey.\(^\text{42}\)

A total of 1625 individuals participated in the IRAS (56% women).\(^\text{43}\) The final study sample included 613 non-Hispanic whites (NHW), 548 Hispanics (His), and 464 African Americans (AA). FSIGT tests were successfully performed in 94% (1525/1625) of IRAS participants overall. Individuals with normal glucose tolerance constituted the largest segment of the study sample (44%) (NHW, \(n = 291\); AA, \(n = 187\); and His, \(n = 241\)), followed by diabetic subjects (33%) (NHW, \(n = 177\); AA, \(n = 176\); and His, \(n = 241\)) and persons with impaired glucose tolerance (23%) (NHW, \(n = 143\); AA, \(n = 101\); and His, \(n = 125\)). The distribution of insulin sensitivity has been recently described in nondiabetic\(^\text{44}\) and diabetic\(^\text{45}\) subjects from the IRAS.

Race and ethnicity were assessed by self-report. Hispanic ethnicity was defined by the US census question, “Are you of Spanish or Hispanic descent?” Height, weight, and girth (minimum waist, waist at the umbilicus and hips) were measured following a standardized protocol. BMI in weight/height\(^2\) (kg/m\(^2\)) was used as an estimate of overall adiposity. The ratio of waist circumference was used as an estimate of body fat distribution.

The IRAS examination required 2 visits (~1 week apart; range, 2 to 28 days), each lasting approximately 4 hours. Oral glucose tolerance tests and FSIGT tests were performed during the first and second visits, respectively. Participants were asked before each visit to fast for 12 hours, to abstain from heavy exercise and alcohol for 24 hours, and to refrain from smoking the morning of the examination. For the oral glucose tolerance test, a 75-g glucose load (Orangedex, Custom Laboratories) was administered in <10 minutes. Blood was collected before ingestion and at 2 hours after the glucose load. Glucose tolerance was classified according to the World Health Organization criteria.\(^\text{46}\) Insulin sensitivity was assessed by the FSIGT test\(^\text{47}\) with minimal model (MINMOD) analysis.

Plasma glucose was measured with the glucose oxidase technique on an automated analyzer (Yellow Springs Equipment Co). Insulin was measured using the dextran-charcoal radioimmunoassay.\(^\text{48}\) This insulin assay cross-reacts with proinsulin. Glucose and insulin levels in all samples were measured at the central IRAS laboratory at the University of Southern California, Los Angeles. The split-pair coefficient of variation (CV) for insulin was 15% in the IRAS (\(n = 86\)).

Fasting serum intact proinsulin and 32-33 split proinsulin were determined from samples stored at ~70°C for an average of 3.3 years (35 to 44 months) by means of highly specific 2-site monoclonal antibody–based immunoradiometric assays.\(^\text{49}\) The split-pair CV was 14% for proinsulin (\(n = 98\)) and 18% for 32-33 split proinsulin (\(n = 98\)). There was no detectable cross-reactivity of insulin or 32-33 split proinsulin in the intact proinsulin assay. Insulin did not significantly cross-react in the assay for 32-33 split proinsulin, and the cross-reactivity of intact proinsulin in this assay was 84%. Assay values of 32-33 split proinsulin were corrected for this by subtraction of the corresponding proinsulin cross-reactivity. The assay of 32-33 split proinsulin cross-reacts equally with 32-33, des-32, and des-31-32 split proinsulins. We used the term 32-33 split proinsulin to indicate the sum of these 3 molecules, the majority of which are des-31-32 split proinsulin.\(^\text{50}\) The sensitivity limit of the intact proinsulin and 32-33 split proinsulin assays was 1.25 pmol/L (3 SDs from zero). Intact proinsulin and 32-33 split proinsulin were determined at the laboratory of the Department of Clinical Biochemistry at Addenbrooke’s Hospital, Cambridge, UK.

Plasma lipoprotein measurements were obtained from single fresh fasting plasma samples using Lipid Research Clinic methods. VLDL was isolated by preparative ultracentrifugation, and VLDL (top) and bottom fractions were measured for cholesterol and triglyceride concentrations. HDL cholesterol was measured after precipitation of apolipoprotein B–containing lipoproteins with MnCl\(_2\) and heparin. The cholesterol content in the supernatant was measured in a separate autoanalyzer channel set to measure low cholesterol values. LDL cholesterol was calculated as the difference between the HDL cholesterol and the bottom cholesterol. Triglycerides were measured enzymatically after correction for free glycerol.

Fibrinogen was measured in citrated plasma with a modified clot-rate assay using the Diagnostica STAGO STF instrument as described.\(^\text{51}\) This is based on the original method of Clauss,\(^\text{52}\) with a CV of 3.0%. Plasminogen activator inhibitor-1 (PAI-1) was also measured in citrated plasma,\(^\text{53}\) using a 2-site immunoassay that is sensitive to free PAI-1 but not to PAI-1 complex with tissue plasminogen activator.\(^\text{54}\) The citrate sample was centrifuged for a minimum of 30 000g minutes to make certain that there was no contamination from platelet PAI-1; the CV was 6.0%.

High-resolution B-mode carotid ultrasonography was performed with Toshiba SSA-270A imaging units (Toshiba America Medical Systems) to provide an index of atherosclerosis.\(^\text{55}\) The scanning and reading protocols were identical to those used in the Cardiovascular Health Study.\(^\text{56}\) All studies were recorded on super VHS tape
### Results

Table 1 shows the characteristics of the nondiabetic subjects by ethnicity. Table 2 shows Spearman correlations (in the overall group) of proinsulin and insulin with IMT, adjusted for age, clinic, ethnic group, sex, and smoking. Proinsulin was significantly correlated with CCA IMT ($P=0.029$) and borderline significantly correlated with ICA IMT ($P=0.057$). Split proinsulin, fasting insulin, 2-hour insulin, and fasting proinsulin/fasting insulin ratio were not significantly correlated with IMT. Because previous analyses from the IRAS suggest a stronger relation between insulin sensitivity and IMT in non-Hispanic whites and Hispanics than African Americans, we next tested whether the relation between proinsulin and IMT might differ between the ethnic groups. The probability value for overall ethnicity ($P=0.017$) suggests a stronger relation between insulin sensitivity and IMT in non-Hispanic whites and Hispanics, respectively.

In Table 3, we show correlations separately in Hispanics and non-Hispanic whites compared with African Americans. These data were adjusted for age, sex, ethnicity, clinic, and smoking status. Proinsulin, split proinsulin, and fasting insulin were significantly correlated with ICA IMT, whereas proinsulin was significantly correlated with CCA IMT in Hispanics and non-Hispanic whites. In contrast, in African Americans, neither insulin nor proinsulin was significantly correlated with IMT.

After further adjustment for LDL cholesterol, HDL cholesterol, triglycerides, LDL size, and PAI-1, the associations between proinsulin and IMT were no longer statistically significant except for ICA IMT in Hispanics ($P=0.019$, CCA=$0.017$).

### Statistical Analyses

Means and standard deviations were presented for the clinical characteristics of the subjects studied. These descriptive statistics were presented separately for each of the 3 ethnic groups studied (Table 1). Next, analyses were performed using correlation and ANCOVA techniques (SAS version 6.08, SAS Institute). Because many of the key variables were not normally distributed (ie, insulin, proinsulin, triglycerides, and PAI-1), we used predominantly non-parametric correlation analyses (Spearman rank correlations) for statistical testing. The initial model adjusted for demographic variables (age, sex, ethnicity, clinic, and smoking status). Further adjustment (using continuous variables) was made for blood pressure, lipid levels (LDL, HDL, triglycerides), LDL size, waist circumference, and PAI-1 in the second model. Because of the large number of comparisons made (especially in Table 2), the nominal probability values should be interpreted with caution.

In these models, we examined whether there were any interactions between proinsulin and either sex or ethnicity. There were no significant interactions with sex; however, significant interactions of proinsulin and ethnicity were observed, such that African Americans had a different relationship of proinsulin and IMT than non-Hispanic whites and Hispanics. Because there was no significant difference in the relation between proinsulin and IMT for non-Hispanic whites and Hispanics, these groups were pooled together in the analyses.

### Table 1. Clinical Characteristics of Nondiabetic Subjects by Ethnic Group

<table>
<thead>
<tr>
<th></th>
<th>African American</th>
<th>Hispanic</th>
<th>Non-Hispanic Whites</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>265</td>
<td>324</td>
<td>394</td>
</tr>
<tr>
<td>Men/women</td>
<td>43/57</td>
<td>42/58</td>
<td>48/52</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>29.4 (5.9)</td>
<td>28.8 (5.9)</td>
<td>27.5 (5.1)</td>
</tr>
<tr>
<td>WHR</td>
<td>0.843 (0.082)</td>
<td>0.873 (0.087)</td>
<td>0.857 (0.087)</td>
</tr>
<tr>
<td>Age, y</td>
<td>54.3 (8.5)</td>
<td>53.9 (8.3)</td>
<td>56.0 (8.3)</td>
</tr>
<tr>
<td>Fasting insulin, pmol/L</td>
<td>101.6 (94)</td>
<td>105.2 (107)</td>
<td>81.1 (67.6)</td>
</tr>
<tr>
<td>2-hour insulin, pmol/L</td>
<td>625 (593)</td>
<td>713 (635)</td>
<td>497 (470)</td>
</tr>
<tr>
<td>Intact proinsulin, pmol/L</td>
<td>6.79 (6.5)</td>
<td>6.28 (5.3)</td>
<td>5.39 (4.6)</td>
</tr>
<tr>
<td>Split proinsulin, pmol/L</td>
<td>8.90 (9.4)</td>
<td>8.90 (7.6)</td>
<td>7.22 (7.8)</td>
</tr>
<tr>
<td>Proinsulin/insulin ratio, pmol/L</td>
<td>0.079 (0.065)</td>
<td>0.070 (0.044)</td>
<td>0.079 (0.061)</td>
</tr>
<tr>
<td>LDL cholesterol, mmol/L</td>
<td>3.79 (0.88)</td>
<td>3.56 (0.94)</td>
<td>3.64 (0.90)</td>
</tr>
<tr>
<td>HDL cholesterol, mmol/L</td>
<td>1.34 (0.42)</td>
<td>1.12 (0.34)</td>
<td>1.22 (0.39)</td>
</tr>
<tr>
<td>Triglyceride, mmol/L</td>
<td>1.18 (0.65)</td>
<td>1.79 (1.13)</td>
<td>1.55 (0.97)</td>
</tr>
<tr>
<td>LDL Systolic blood pressure, mm Hg</td>
<td>263.2 (8.9)</td>
<td>259.3 (9.4)</td>
<td>260.4 (10.2)</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>126.15 (165)</td>
<td>120.1 (168)</td>
<td>121.6 (173)</td>
</tr>
<tr>
<td>Fibrinogen, mg/dL</td>
<td>78.8 (9.8)</td>
<td>78.3 (8.9)</td>
<td>76.5 (9.1)</td>
</tr>
<tr>
<td>PAI-1, ng/mL</td>
<td>14.5 (12.6)</td>
<td>28.1 (24.0)</td>
<td>21.1 (19.6)</td>
</tr>
<tr>
<td>Fasting glucose, mmol/L</td>
<td>5.64 (0.70)</td>
<td>5.38 (0.55)</td>
<td>5.47 (0.62)</td>
</tr>
<tr>
<td>2-Hour glucose, mmol/L</td>
<td>7.01 (1.91)</td>
<td>6.96 (1.92)</td>
<td>6.89 (1.83)</td>
</tr>
<tr>
<td>CCA IMT, μm</td>
<td>856 (221)</td>
<td>738 (158)</td>
<td>799 (194)</td>
</tr>
<tr>
<td>ICA IMT, μm</td>
<td>908 (361)</td>
<td>775 (288)</td>
<td>851 (392)</td>
</tr>
</tbody>
</table>

Values are mean (SD) or percentage.
Americans are very insulin resistant,40 and possibly a plateau in insulin to atherosclerosis should differ in African Americans, why the relationship of insulin resistance, insulin, and proinflammatory markers characterizes the association of insulin or proinsulin to atherosclerosis is not clear. Proinsulin is present in low concentrations and has no significant role in cardiovascular risk factors in both diabetic25,26 and non-diabetic27,28 subjects. When cardiovascular risk factors were adjusted for 1 at a time, adjustment for PAI-1 markedly attenuated the association between proinsulin and IMT, suggesting a possible role for PAI-1 in mediating this association. Proinsulin (at very high concentrations) has been shown to increase PAI-1 in an in vitro system.55,56 Increased levels of PAI-1 have been associated with myocardial infarction.57,58

The relation of proinsulin to CHD is controversial. Small cross-sectional studies have found inconsistent relations between proinsulin and CHD, with some studies reporting significant results31,32 and 1 study reporting no significant association.30 In 1 longitudinal study,32 no significant relations were found between proinsulin and CHD.

The explanation for the possible role of proinsulin in atherosclerosis is not clear. Proinsulin is present in low concentrations except in diabetic subjects.17-24 Furthermore, the activity of proinsulin either in vitro or in vivo is only 8% to 10% of that of insulin,59 so these low concentrations are unlikely to have a biological insulin-like effect. Recently, Alessi et al60 have reported increased production of PAI-1 by visceral fat, suggesting that visceral fat may affect both insulin resistance and increased PAI-1. The above study may suggest that a common factor (perhaps visceral fat) increases proinsulin, PAI-1, and IMT, rather than suggesting that increased proinsulin might lead to increased PAI-1, which in turn might lead to increased IMT. However, when we adjusted for the effect of BMI and WHR, the relation between proinsulin and IMT remained significant, suggesting that the relation between proinsulin and IMT is at least partially independent of adiposity.

Another possibility for the association between proinsulin and IMT might be autonomic dysfunction. Autonomic dysfunction has been shown to predict cardiovascular mortality.61,62 Recently, increased proinsulin levels have been associated with the sympathovagal balance of the autonomic nervous function in both non–insulin-dependent diabetes mellitus patients and control subjects.63,64

In conclusion, we have shown a significant (but modest) association between proinsulin and atherosclerosis that may be mediated in part by higher PAI-1 levels. The association between proinsulin and IMT appears to be stronger than that of insulin and IMT. The biological significance of the association between proinsulin and IMT is unknown, and thus

### Discussion

In this report, we found a significant association between proinsulin concentrations and carotid IMT. The relation of intact proinsulin to atherosclerosis was stronger than the relation of insulin or split proinsulin to atherosclerosis. The association between proinsulin and IMT was stronger in Hispanics and non-Hispanic whites than in African Americans.16 In fact, the correlation between proinsulin and CCA and ICA IMT remained statistically significant (data not shown).

We do not have a biologically plausible explanation why the relationship of insulin resistance, insulin, and proinsulin to atherosclerosis should differ in African Americans, but we have shown previously that nondiabetic African Americans are very insulin resistant,40 and possibly a plateau might characterize the association of insulin or proinsulin to atherosclerosis. Two previous small studies have examined the relation of proinsulin to atherosclerosis. Katz et al40 did not find a significant relation between proinsulin and insulin and atherosclerosis (as assessed by coronary angiography) in a predominantly African American population. Niskanen et al40 also did not find an association between proinsulin concentrations and IMT in a Finnish population. The differences in the studies may all relate to the error in the assay for proinsulin or insulin and the number of participants, since both will have relatively large effects on associations as assessed by correlation analyses. This might be especially true if the r values are as small as they are here. However, in the IRAS the precision of the proinsulin and insulin assays were similar as determined by the split-pair CVs.

In our data, the relation between levels of insulin and proinsulin and carotid IMT was no longer statistically significant after adjustment for cardiovascular risk factors. Previous work has suggested that proinsulin may be strongly associated with cardiovascular risk factors in both diabetic25,26 and non-diabetic27,28 subjects. When cardiovascular risk factors were adjusted for 1 at a time, adjustment for PAI-1 markedly attenuated the association between proinsulin and IMT, suggesting a possible role for PAI-1 in mediating this association. Proinsulin (at very high concentrations) has been shown to increase PAI-1 in an in vitro system.55,56 Increased levels of PAI-1 have been associated with myocardial infarction.57,58

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### Table 3. Spearman Correlations (P) With IMT of Carotid Arteries Separately for Non-Hispanic Whites and Hispanics Combined and African Americans, Adjusted for Age, Clinic, Sex, and Smoking Status

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</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CCA</td>
<td>ICA</td>
</tr>
<tr>
<td>Proinsulin</td>
<td>0.087</td>
<td>0.101</td>
</tr>
<tr>
<td>Split proinsulin</td>
<td>0.059</td>
<td>0.092</td>
</tr>
<tr>
<td>Fasting insulin</td>
<td>0.049</td>
<td>0.087</td>
</tr>
<tr>
<td>2-Hour insulin</td>
<td>0.063</td>
<td>0.062</td>
</tr>
<tr>
<td>Proinsulin/insulin</td>
<td>0.047</td>
<td>0.008</td>
</tr>
</tbody>
</table>

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In conclusion, we have shown a significant (but modest) association between proinsulin and atherosclerosis that may be mediated in part by higher PAI-1 levels. The association between proinsulin and IMT appears to be stronger than that of insulin and IMT. The biological significance of the association between proinsulin and IMT is unknown, and thus
it is possible that the relation between proinsulin and atherosclerosis may be an epiphenomenon. Further work on the biological basis of this association is necessary.

Acknowledgments
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References


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