Diabetes and Progression of Carotid Atherosclerosis  
The Insulin Resistance Atherosclerosis Study

Lynne E. Wagenknecht, Daniel Zaccaro, Mark A. Espeland, Andrew J. Karter,  
Daniel H. O’Leary, Steven M. Haffner

Objective—We sought to determine the rate of progression of carotid atherosclerosis in persons with normal glucose tolerance, impaired glucose tolerance, and undiagnosed and diagnosed type 2 diabetes.

Methods and Results—The Insulin Resistance Atherosclerosis Study (IRAS) is an observational cohort study in which 1192 men and women were examined at a 5-year interval. Participants of 3 ethnic groups (non-Hispanic white, African American, and Hispanic) were selected from the general population to represent a range of glucose tolerance. Baseline and follow-up ultrasound studies were obtained to estimate progression of common carotid artery (CCA) and internal carotid artery (ICA) intimal-medial thickness (IMT). Baseline glucose tolerance status was defined by an oral glucose tolerance test and World Health Organization criteria. In persons with normal glucose tolerance, progression of CCA IMT was 3.8 μm/y, and ICA IMT, 17.7 μm/y. In both CCA and ICA, progression of IMT, unadjusted for cardiovascular disease (CVD) risk factors, was approximately twice the rate in persons with diabetes than in those with normal or impaired glucose tolerance. Adjustment for CVD risk factors attenuated these differences somewhat in both sites of the carotid artery. Persons with undiagnosed diabetes had a greater ICA IMT progression rate than did persons with diagnosed diabetes (33.9 μm/y vs 26.6 μm/y, P=NS). Progression rates did not differ between persons with normal and impaired glucose tolerance.


Key Words: diabetes ■ atherosclerosis ■ epidemiology ■ prevention ■ ultrasound

Cardiovascular disease (CVD) risk is increased 2- to 4-fold in persons with diabetes relative to those without.1–3 Possible mechanisms for this increased risk include hypertension, dyslipidemia, hyperglycemia, and insulin resistance. Cross-sectional carotid artery intimal-medial thickness (IMT) is a powerful predictor of future CVD events.4,5 Progression of IMT has also been shown to predict coronary events in men who have undergone coronary artery bypass graft surgery.6

We have reported previously, from a cross-sectional analysis in the Insulin Resistance Atherosclerosis Study (IRAS), that common carotid artery (CCA) IMT was approximately 70 μm greater and internal carotid artery (ICA) IMT was 130 μm greater in persons with established diabetes relative to those with normal glucose tolerance (NGT), after adjustment for CVD risk factors.7 Average IMT (CCA and ICA) of persons with undiagnosed diabetes did not differ from the IMT of persons with NGT.

To date, only 1 longitudinal analysis has been published that compared the rates of progression of carotid wall IMT in persons with diabetes relative to those without.8 These investigators have reported a more rapid rate of progression among persons with diabetes. The rate of progression of IMT in undiagnosed diabetes versus diagnosed diabetes (as defined by oral tolerance test [OGTT]) is also of interest but has not been reported. Five years of IRAS follow-up data were examined to assess the progression of carotid IMT across these diagnostic categories.

Methods.

The IRAS is a multicenter, observational, epidemiological study of the relations among insulin resistance, CVD, and risk factors in a multietnic cohort with varying states of glucose tolerance. The design and methods of this study have been described in detail.9 In brief, the study was conducted at 4 clinical centers. At centers in Oakland and Los Angeles, California, non-Hispanic whites and African Americans were recruited from Kaiser Permanente, a nonprofit health maintenance organization. Centers in San Antonio, Tex, and San Luis Valley, Colo, recruited whites and Hispanics from 2 ongoing population-based studies (the San Antonio Heart Study and the San Luis Valley Diabetes Study). The sample was recruited to

Received February 28, 2003; revision accepted March 28, 2003. 
From the Department of Public Health Sciences (L.E.W., D.Z., M.A.E.), Wake Forest University School of Medicine, Winston-Salem, NC; the Division of Research (A.J.K.), Kaiser Permanente, Oakland, Calif; the Department of Radiology (D.H.O.’L.), New England Medical Center, Boston, Mass; and the University of Texas Health Sciences Center (S.M.H.), San Antonio.

Correspondence to Lynne E. Wagenknecht, DrPH, Department of Public Health Sciences, Wake Forest University School of Medicine, Medical Center Boulevard, Winston-Salem, NC 27157-1063. E-mail lwgnkcht@wfubmc.edu

© 2003 American Heart Association, Inc.

Arterioscler Thromb Vasc Biol is available at http://www.atvbaha.org

DOI: 10.1161/01.ATV.0000072273.67342.6D
meet a goal of nearly equal numbers of persons with NGT, impaired glucose tolerance (IGT), and known type 2 diabetes. Persons taking insulin were excluded. A total of 1624 individuals participated in the baseline IRAS examination (56% women), which occurred between October 1992 and April 1994. After a planned 5-year time period, during which annual contact was made with the participants, follow-up examinations were conducted with the protocol that was used at baseline. The IRAS protocol was approved by local institutional review boards, and all participants provided written, informed consent.

The IRAS protocol required 2 visits, 1 week apart, of ~4 hours each. Participants were asked to fast for 12 hours before each visit, to abstain from heavy exercise and alcohol for 24 hours, and to refrain from smoking on the morning of the examination. During the first visit, a 75-g OGTT was administered, with fasting and 2-hour postload blood samples being collected. Glucose tolerance status was determined at baseline by World Health Organization criteria. Specifically, NGT was defined as fasting glucose (FG) and 2-hour glucose <140 mg/dL. IGT was defined as FG <140 mg/dL and 2-hour glucose ≥140 and <200 mg/dL. Diabetes was defined as FG ≥140 mg/dL or 2-hour glucose ≥200 mg/dL. Participants whose OGTT results met these criteria for diabetes but who did not report having been told by a doctor that they had diabetes were considered to have undiagnosed diabetes. Those whose OGTT results met these criteria for diabetes and who reported having been told that they had diabetes were classified as diagnosed diabetes. Participants taking oral hypoglycemic medications were considered to have diagnosed diabetes, regardless of their OGTT results or their report of a previous diagnosis. All participants also provided information regarding their past and current use of antihypertensive and lipid-lowering medications.

Height and weight were measured to the nearest 0.5 cm and 0.1 kg, respectively. Body mass index was calculated as weight/height$^2$ (kg/m$^2$) and was used as an estimate of overall adiposity. Waist circumference, a validated estimate of visceral adiposity, was measured to the nearest 0.5 cm. Duplicate circumference measurements were made by following a standardized protocol, with averages used in the analysis. Ethnicity and smoking status were assessed by self-report. Hypertension was defined as systolic blood pressure >140 mm Hg, diastolic blood pressure >90 mm Hg, and/or self-report of antihypertensive medication use. Plasma glucose was measured with the glucose oxidase technique on an autoanalyzer. Serum insulin was measured with a dextran-charcoal radioimmunoassay, which has a 19% external coefficient of variation. Serum intact pro-insulin was measured by using a highly specific, 2-site monoclonal antibody–based immunoradiometric assay. LDL cholesterol was measured directly with the $\beta$-quantification procedure. LDL size distribution (ie, distribution of diameters of the major LDL peaks) was determined with the method of Krauss and Burke on gradient gels obtained from Isolab. Insulin sensitivity was determined by using an insulin-boosted, frequently sampled intravenous GTT. A reduced sampling protocol was used. Insulin sensitivity, expressed as a insulin sensitivity index ($S_2$), was calculated by mathematical modeling methods (MINMOD, version 3.0).

High-resolution B-mode carotid ultrasonography was performed at baseline and follow-up IRAS examinations with an identical scanning protocol and identical equipment. A bilateral assessment of wall thickness was made of the ICA and the CCA. For the ICA, the sonographer sought the site of maximal thickness in the region between the dilatation of the carotid bulb and the ICA. 1 cm distal to the tip of the flow divider. Three images were obtained bilaterally at the site of maximal thickness at different interrogation angles (proximal, lateral, and anterior) and at the near and far walls. At follow-up, the sonographer sought the site of maximal IMT, independent of its location at baseline. For the CCA, bilateral images were obtained 1 cm proximal to the dilatation of the carotid bulb at a single (lateral) angle. This protocol resulted in up to 8 measurements in each of the right and left arteries for a possible total of 16 measurements on each participant at each examination.
TABLE 1. Baseline Characteristics of the IRAS Cohort (1992 to 1994) Grouped by Baseline Glucose Tolerance Status:

<table>
<thead>
<tr>
<th></th>
<th>Normal (n=553)</th>
<th>IGT (n=273)</th>
<th>Undiagnosed Diabetes (n=138)</th>
<th>Diagnosed Diabetes (n=228)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>53.7 (8.5)</td>
<td>56.6 (7.9)</td>
<td>56.6 (8.2)</td>
<td>56.7 (8.1)</td>
</tr>
<tr>
<td>Sex, % male</td>
<td>46.1</td>
<td>37.4</td>
<td>42.8</td>
<td>48.7</td>
</tr>
<tr>
<td>Ethnicity, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Hispanic white</td>
<td>40.0</td>
<td>40.3</td>
<td>37.7</td>
<td>33.3</td>
</tr>
<tr>
<td>African American</td>
<td>26.6</td>
<td>28.6</td>
<td>36.2</td>
<td>31.6</td>
</tr>
<tr>
<td>Hispanic American</td>
<td>33.5</td>
<td>31.1</td>
<td>26.1</td>
<td>35.1</td>
</tr>
<tr>
<td>Hypertensive, %</td>
<td>25.8</td>
<td>40.7</td>
<td>56.5</td>
<td>51.8</td>
</tr>
<tr>
<td>Current smoker, %</td>
<td>14.6</td>
<td>11.4</td>
<td>18.2</td>
<td>14.0</td>
</tr>
<tr>
<td>Past smoker, %</td>
<td>39.1</td>
<td>39.2</td>
<td>41.6</td>
<td>46.1</td>
</tr>
<tr>
<td>LDL, mmol/L*</td>
<td>3.60 (0.89)</td>
<td>3.72 (0.93)</td>
<td>3.70 (0.93)</td>
<td>3.55 (0.89)</td>
</tr>
<tr>
<td>LDL size, Å</td>
<td>261 (9)</td>
<td>260 (10)</td>
<td>257 (9)</td>
<td>257 (10)</td>
</tr>
<tr>
<td>TG, mmol/L*</td>
<td>1.38 (0.94)</td>
<td>1.74 (1.05)</td>
<td>2.02 (1.33)</td>
<td>2.26 (2.24)</td>
</tr>
<tr>
<td>HDL, mmol/L*</td>
<td>1.25 (0.40)</td>
<td>1.17 (0.38)</td>
<td>1.10 (0.31)</td>
<td>1.02 (0.29)</td>
</tr>
<tr>
<td>Waist, cm</td>
<td>87.7 (11.5)</td>
<td>94.6 (13.6)</td>
<td>100.2 (12.3)</td>
<td>98.4 (11.9)</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>27.3 (4.7)</td>
<td>30.4 (6.5)</td>
<td>32.7 (6.0)</td>
<td>31.0 (5.7)</td>
</tr>
<tr>
<td>Sₐ 10⁻⁴×min⁻¹×μU⁻¹×mL⁻¹</td>
<td>2.6 (2.1)</td>
<td>1.29 (1.2)</td>
<td>0.54 (0.82)</td>
<td>0.54 (0.82)</td>
</tr>
<tr>
<td>Fasting glucose, mmol/L*</td>
<td>5.29 (0.56)</td>
<td>5.82 (0.62)</td>
<td>6.13 (2.50)</td>
<td>10.79 (3.35)</td>
</tr>
<tr>
<td>Fasting insulin, pmol/L</td>
<td>94.5 (68.1)</td>
<td>135.4 (153.5)</td>
<td>184.0 (142.4)</td>
<td>152.8 (93.1)</td>
</tr>
<tr>
<td>Pro-insulin, pmol/L</td>
<td>5.1 (4)</td>
<td>7.9 (7)</td>
<td>16.6 (17.7)</td>
<td>20 (15.1)</td>
</tr>
<tr>
<td>PAI-1, ng/mL</td>
<td>20.3 (21.7)</td>
<td>25.0 (20.4)</td>
<td>32.6 (21.6)</td>
<td>32.5 (26.0)</td>
</tr>
<tr>
<td>CCA IMT, μm</td>
<td>791 (226)</td>
<td>824 (186)</td>
<td>890 (238)</td>
<td>907 (256)</td>
</tr>
<tr>
<td>ICA IMT, μm</td>
<td>900 (406)</td>
<td>924 (394)</td>
<td>909 (361)</td>
<td>1050 (487)</td>
</tr>
<tr>
<td>Follow-up time, y</td>
<td>5.26 (0.29)</td>
<td>5.26 (0.33)</td>
<td>5.20 (0.28)</td>
<td>5.23 (0.32)</td>
</tr>
</tbody>
</table>

Values are mean (SD) or percent.

*To convert LDL or HDL from millimoles per liter to milligrams per deciliter, divide millimoles per liter by 0.0259. To convert triglycerides from millimoles per liter to milligrams per deciliter, divide millimoles per liter by 0.0113. To convert glucose from millimoles per liter to milligrams per deciliter, divide millimoles per liter by 0.0555.

†P<0.05 for difference between undiagnosed diabetes and diagnosed diabetes.

Risk factors for atherosclerosis worsened across categories of poorer glucose tolerance at baseline (Table 1). Persons with undiagnosed diabetes at baseline tended to have a similar risk profile to those with diagnosed diabetes, with the exception of body mass index and fasting insulin, which were greater in persons with undiagnosed diabetes. Persons with undiagnosed diabetes were also more likely to be hypertensive and current smokers, though not significantly so. The average duration of diabetes was 6.8 years (SD, 6.4 years) in those with diagnosed diabetes. Persons with IGT had risk profiles notably worse than those with NGT. At baseline, ICA IMT (but not CCA IMT) was greater in diagnosed than undiagnosed diabetics.

There was no difference in baseline use of lipid-lowering medications across the 4 groups (Table 2). The use of antihypertensive medications did not differ across the 2 diabetes groups but was notably lower in those with NGT. Nearly three fourths of diagnosed diabetics reported taking oral hypoglycemics. None was taking insulin at baseline, because it was an exclusion criterion for enrollment in IRAS. At follow-up, those with undiagnosed diabetes (at baseline) were less likely to be taking hypoglycemic medications than were diagnosed diabetics. Their use of lipid-lowering and antihypertensive medications was lower, but not significantly so.

The average CCA IMT progression rate (SE), adjusted for demographic factors, was 3.8 (1.3) μm/y in persons with NGT and 4.2 (1.8) μm/y in persons with IGT (Figure 1, model 1). Average CCA IMT progression was nearly 2 times greater in persons with diabetes (7.5 (2.6) μm/y and 7.2 (1.9) μm/y in persons with undiagnosed and diagnosed diabetes, respectively). On adjustment for CVD risk factors, a graded relation was observed with CCA IMT progression rates: lowest in persons with NGT, intermediate in persons with IGT, and greatest in persons with diagnosed diabetes (4.2, 4.6, 5.6, and 6.5 μm/y; model 2). In this multivariable model, glucose tolerance status was highly predictive of CCA IMT progression (P=0.008), as was age (P<0.0001), sex (P<0.0001), current smoking (P=0.001), and hypertension (P=0.01). Additional adjustment for use of medications at follow-up (model 3) had no impact on the estimates of CCA IMT progression (not shown).

The average ICA IMT progression rate, adjusted for demographic factors, was 17.7 (1.7) μm/y in persons with NGT and 16.9 (2.5) μm/y in persons with IGT (Figure 2, model 1). Average ICA IMT progression was approximately 2 times greater in persons with diabetes, with the undiagnosed group having the greatest average progression rate [36.0 (3.6) μm/y] compared with persons with diagnosed diabetes [30.4...
This trend persisted after adjustment for CVD risk factors, with the lowest ICA IMT progression rates observed in those with NGT and IGT (19.6 and 16.9 μm/y, respectively), intermediate in persons with diagnosed diabetes (26.6 μm/y), and highest in persons with undiagnosed diabetes (33.9 μm/y; model 2). The difference in progression rates between persons with diagnosed and undiagnosed diabetes was not statistically significant ($P=0.15$). In this multivariate model, glucose tolerance status was predictive of ICA IMT progression ($P<0.001$), as was age ($P<0.0001$), sex ($P<0.0001$), LDL ($P=0.002$), past smoking ($P=0.002$), current smoking ($P<0.0001$), and hypertension ($P=0.003$). Further adjustment for use of medications at follow-up (model 3) had no impact on the estimates of ICA IMT progression (not shown).

**Discussion**

We have observed an increased rate of progression of carotid atherosclerosis in persons with diabetes relative to those without diabetes. In both the CCA and ICA, mean progression of IMT was approximately 2 times greater in persons with diabetes than in those with NGT or IGT. No difference was observed in progression rates between those with NGT and IGT. However, a trend toward a greater rate of progression among persons with undiagnosed diabetes relative to diagnosed diabetes was observed in the ICA ($P=0.15$).

Although it is well documented that increased IMT at baseline predicts an increased risk of future CVD events, few data are available indicating that an increased rate of progression of IMT predicts an increased risk of CVD events. In 1 report of a high-risk population of 146 men who had undergone coronary artery bypass surgery, an increased rate of progression predicted a higher rate of coronary events. On the basis of regression analyses, the authors estimated that each 30-μm/y increase in CCA IMT was associated with an increased risk for nonfatal myocardial infarction or coronary death of 2.2-fold and for nonfatal myocardial infarction, coronary death, or revascularization procedure of 3.1-fold. Baseline IMT also predicted future events in this small cohort. This limited study suggests that an increased rate of progression of IMT is associated with future clinical events.

Type 2 diabetes was associated with an increased rate of progression of carotid IMT in this cohort. In our review, we found only 1 other study that has examined this question in a longitudinal analysis. Chambless and colleagues, in a report from the Atherosclerosis Risk In Communities (ARIC) co-

---

**TABLE 2. Medication Use (%) as Self-Reported at Baseline and Follow-Up by Baseline Glucose Tolerance Status**

<table>
<thead>
<tr>
<th>Medication Class</th>
<th>Normal (n=553)</th>
<th>IGT (n=273)</th>
<th>Undiagnosed Diabetes (n=138)</th>
<th>Diagnosed Diabetes (n=228)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral hypoglycemic</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>74.6†</td>
</tr>
<tr>
<td>Insulin*</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Antihypertensive</td>
<td>17.0</td>
<td>32.6</td>
<td>39.1</td>
<td>40.4</td>
</tr>
<tr>
<td>Lipid lowering</td>
<td>5.8</td>
<td>10.3</td>
<td>8.0</td>
<td>9.6</td>
</tr>
<tr>
<td>Follow-up</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral hypoglycemic</td>
<td>0.5</td>
<td>5.5</td>
<td>38.4</td>
<td>75.9†</td>
</tr>
<tr>
<td>Insulin</td>
<td>0</td>
<td>0</td>
<td>2.2</td>
<td>22.8†</td>
</tr>
<tr>
<td>Antihypertensive</td>
<td>26.0</td>
<td>41.8</td>
<td>44.2</td>
<td>52.6</td>
</tr>
<tr>
<td>Lipid lowering</td>
<td>12.1</td>
<td>19.0</td>
<td>15.9</td>
<td>23.7</td>
</tr>
</tbody>
</table>

*Persons taking insulin were excluded from participation in IRAS at the baseline examination.
†$P<0.0001$ for difference between undiagnosed diabetes and diagnosed diabetes. No other differences met statistical significance, $P<0.05$.

---

Figure 1. Progression rate (μm/y) and SE of CCA IMT by glucose tolerance status. Model 1 was fitted with adjustment for varying progression rates among demographic factors (age, sex, clinic, and ethnicity). Model 2 included adjustment for demographic factors and risk factors (LDL, triglycerides, LDL size, hypertension, smoking, waist girth, and pro-insulin).
hort, reported that CCA IMT increased \(\approx 10 \mu m/y\) in persons with diabetes compared with \(\approx 8 \mu m/y\) in persons without diabetes. Numerous other cross-sectional studies have reported that carotid IMT is greater in persons with diabetes than in those without. In the ARIC cohort, IMT was \(\approx 70 \mu m\) thicker in participants with diabetes. Similar findings have been reported in the elderly Cardiovascular Health Study cohort and in a cross-sectional analysis of data from the IRAS cohort.\(^7\)

Atherosclerosis is presumed to be accelerated in diabetes for a number of reasons. First, diabetes is associated with an increased risk of traditional coronary heart disease (CHD) risk factors, including hypertension, dyslipidemia, obesity, and hyperinsulinemia. Although these risk factors act as independent contributors to CHD in persons with diabetes, they account for no more than 25% of the excess CHD risk in diabetes. Our finding is consistent with this; adjustment for these factors (and others) in our models explained very little of the excess risk of IMT progression. Other metabolic disturbances unique to diabetes, such as increased levels of circulating glucose, advanced glycation end products, and oxidation of lipoproteins, might also increase the risk and rate of atherosclerosis.

In the present analysis, ICA IMT appeared to progress at a greater rate among persons with undiagnosed diabetes than in those with diagnosed diabetes. This provocative observation, albeit nonsignificant \((P=0.15)\), deserves further exploration. There are several possible explanations. One is that atherosclerosis progresses more rapidly in the earliest stages of diabetes. In this prodromal stage, glucose and insulin levels are elevated. Insulin is known to have several atherogenic properties. Insulin in physiological concentrations stimulates the proliferation of smooth muscle cells and increases lipid activity and synthesis. High levels of glucose can damage or alter the endothelial barrier, thus allowing insulin to interact with the underlying smooth muscle cells. In a classic experiment, infusion of low-dose insulin directly into the femoral artery of the dog caused marked intimal and medial proliferation with accumulation of cholesterol and fatty acids. In the present analysis, we adjusted separately for fasting insulin concentrations and pro-insulin concentrations and found that pro-insulin explained more of the difference in progression rates between the undiagnosed and diagnosed diabetics than did insulin. (We have previously reported a similar relation between pro-insulin and cross-sectional IMT measures.)\(^23\) In addition to hyperinsulinemia, persons with undiagnosed diabetes also had a greater body mass index relative to those with diagnosed diabetes \((P<0.01)\) and other nonsignificant increases in CVD risk factors, including current smoking, prevalence of hypertension, and LDL concentrations. Statistical adjustment for these factors only accentuated the difference in progression rates between the 2 diabetes groups.

Another explanation for the observed decrease in the rate of ICA IMT progression in the diagnosed group (relative to the undiagnosed group) is survival bias. Such a bias could have resulted from increased mortality (or morbidity) in the group with diagnosed diabetes, whose ICA IMT progressed most rapidly during the 5-year follow-up period, thereby lowering the mean progression rate in this group of survivors who were able to participate in the follow-up IRAS examination. Although the group with diagnosed diabetes did experience the highest death rate, it is unknown whether these persons had rapidly progressing ICA IMT. Thus, such a hypothesis cannot be tested.

An alternative explanation to the lower rate of IMT progression in the group with diagnosed diabetes relative to the undiagnosed group is that treatment with hypoglycemic, antihypertensive, and lipid-lowering medications, hypothesized to be more frequent among the diagnosed group, slowed IMT progression. In fact, there was no difference in current use of antihypertensive and lipid-lowering medications between the undiagnosed and diagnosed groups at baseline. These are medications that have been shown to slow IMT progression.\(^29\)–\(^31\) However, at follow-up (and presumably during the period between baseline and follow-up), use of these drugs was nonsignificantly higher in the diagnosed group. The diagnosed group was also more likely to be using hypoglycemic medications at follow-up (and at baseline, by definition). In fact, only slightly more than half (64%) of the persons with undiagnosed diabetes at baseline were aware of (and/or were being treated for) their diabetes at follow-up.
Regardless, there is no evidence that hypoglycemic medications slow IMT progression. Statistical adjustment for the use of these medications had no impact on the difference in IMT progression rates between groups.

In many studies, duration of diabetes is positively associated with risk of CHD.\textsuperscript{32,33} However, in the Whitehall study,\textsuperscript{34} persons with newly diagnosed diabetes were at increased risk of CHD events relative to persons with previously diagnosed diabetes. The relative risk of CHD death among the newly diagnosed was 3.9, and among the previously diagnosed, \( \approx 2.0 \) relative to the normoglycemic group. Statistical adjustment for major risk factors reduced the effect considerably, yet the highest relative risk remained in the newly diagnosed group.

We did not observe a difference in the progression rates between those with NGT and IGT. We had hypothesized that persons with IGT would have an increased rate of progression owing to their atherogenic risk factor profile. This risk factor profile has been reported by others,\textsuperscript{35} yet IGT state has not been consistently associated cross-sectionally with increased IMT.\textsuperscript{7,36,37} The lack of such a finding might suggest that a lengthy exposure (latent) period might be required for IMT thickening related to the cluster of risk factors characteristic of IMT. Evidence from clinical trials, however, indicates that intervention effects on IMT thickening are evident in periods of time of 2 years or less. It might be that risk factors must reach a threshold to promote such thickening. Alternatively, the lack of a relation with IMT progression could result from misclassification of the IGT state, which is often transient.

The rate of progression of CCA IMT among IRAS participants with NGT can be compared with others reported in the literature. Byington\textsuperscript{38} reviewed 8 lipid-lowering trials and reported annual rates of IMT progression in the placebo groups. In 7 trials reporting progression rates for CCA, the rates ranged from 8 to 46 \( \mu \text{m/y} \). These rates are higher than the rate we report for the CCA (4 \( \mu \text{m/y} \)) and might reflect the atherogenic risk factor profile required of participants in those trials. A more appropriate comparison would be population-based cohort studies. In the ARIC study, progression rates of mean CCA IMT were 6.5 to 10.1 \( \mu \text{m/y} \) across the 4 race-sex groups.\textsuperscript{39} In the Kuopio Ischemic Heart Disease Risk Factor Study of 1026 men aged 42 to 60 years, the progression rate of mean CCA IMT was 28 \( \mu \text{m/y} \).\textsuperscript{39} The broad range of rates for CCA IMT largely reflects differences in the populations studied and in the scanning and reading protocols.

The differing rates of progression in the CCA versus the ICA and the observed differences in relation to glucose tolerance status deserve comment. The literature contrasting IMT progression rates across multiple carotid sites is limited. Progression of atherosclerotic plaque was more rapid in the ICA than the CCA in the Bruneck population-based survey,\textsuperscript{40} although the difference was not as pronounced as we have shown in IRAS for IMT. Furthermore, site-specific differences in risk factor relations have been noted previously.\textsuperscript{41} Hedblad and colleagues\textsuperscript{30} reported that a \( \beta \)-blocker (metoprolol) slowed IMT progression in the bifurcation segment but had little apparent effect on IMT progression in the common segment, whereas a statin (fluvastatin) slowed progression in the common segment. The ICA has been noted to be more susceptible to early atherosclerosis than the CCA,\textsuperscript{42} which might explain the increased progression rates in the undiagnosed diabetics. This region of the carotid artery is subject to lower wall shear stress and focal atherosclerotic lesions linked to lipid accumulation and thrombotic events, whereas in the CCA, atherosclerosis is manifested by diffuse thickening. The present study might add to this literature and suggest that early events and metabolic characteristics of type 2 diabetes (as exhibited in those with undiagnosed diabetes) play an important role in the accelerated progression of ICA IMT. Finally, CCA and ICA IMTs are nearly equivalent in their prediction of subsequent risk of myocardial infarction and stroke.\textsuperscript{5,43}

In conclusion, the progression of carotid atherosclerosis is accelerated in persons with type 2 diabetes in IRAS. This increased rate of atherosclerosis was partially explained by the atherogenic risk factor profile associated with diabetes. Persons with undiagnosed diabetes are at even greater risk of accelerated atherosclerosis in the ICA. With 16 million Americans with diabetes, one third of whom are undiagnosed,\textsuperscript{44} the impact of this finding is significant. Early diagnosis, treatment, and control of blood glucose might reduce this risk, as well as the intensified screening, prevention, and management of CVD risk factors that accompany diabetes.

**Acknowledgments**

This study was supported by grants from the National Heart, Lung, and Blood Institute, Bethesda, Md (U01-HL47887, U01-HL47889, U01-HL47890, U01-HL47892, and U01-HL47902).

**References**

11. Lemaux S, Prudhomme D, Bouchard C, Tremblay A, Despres J-P. A single threshold value of waist girth identifies normal weight and over-


Diabetes and Progression of Carotid Atherosclerosis. The Insulin Resistance Atherosclerosis Study
Lynne E. Wagenknecht, Daniel Zaccaro, Mark A. Espeland, Andrew J. Karter, Daniel H. O'Leary and Steven M. Haffner

Arterioscler Thromb Vasc Biol. published online April 17, 2003;
Arteriosclerosis, Thrombosis, and Vascular Biology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2003 American Heart Association, Inc. All rights reserved.
Print ISSN: 1079-5642. Online ISSN: 1524-4636

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://atvb.ahajournals.org/content/early/2003/04/17/01.ATV.0000072273.67342.6D.citation

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Arteriosclerosis, Thrombosis, and Vascular Biology can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Arteriosclerosis, Thrombosis, and Vascular Biology is online at:
http://atvb.ahajournals.org//subscriptions/