Impaired Glucose Tolerance, Type 2 Diabetes, and Carotid Wall Thickness

The Insulin Resistance Atherosclerosis Study

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OBJECTIVE — To assess whether people with impaired glucose tolerance (IGT) exhibit an increased risk of atherosclerosis as measured by the thickness of the carotid artery.

RESEARCH DESIGN AND METHODS — We examined the relationship between glucose tolerance status and subclinical atherosclerosis in the Insulin Resistance Atherosclerosis Study (IRAS). The IRAS is an epidemiological study of 1,625 Hispanic, African-American, and white men and women, with approximately equal numbers of subjects with normal glucose tolerance (NGT), IGT, and type 2 diabetes as assessed by an oral glucose tolerance test. Half of those with diabetes were previously unaware of their condition and were defined as having new diabetes. Persons using insulin were excluded. The intima-media thickness (IMT) of the common carotid artery (CCA) and internal carotid artery (ICA) was measured as an index of subclinical atherosclerosis using B-mode ultrasonography.

RESULTS — Adjusted for demographics and smoking, CCA-IMT increased most notably at the level of established diabetes (802, 822, 831, and 896 μm for NGT, IGT, new diabetes, and established diabetes, respectively). Adjustment for coronary heart disease (CHD) risk factors, which tended to worsen across glucose tolerance category, further minimized the slightly graded relationship. The relationship with the ICA-IMT was steeper and again suggested that the increased wall thickness is associated with diabetes, not with IGT. The relationship between glucose tolerance category and IMT was similar in men and women.

CONCLUSIONS — We observed considerably greater IMT among persons with established diabetes but no significant increase in persons with IGT. These data suggest that the increased risk of CHD observed in persons with diabetes may largely develop after the onset of overt diabetes.

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Abbreviations: ARIC, Atherosclerosis Risk in Communities; CCA, common carotid artery; CHD, coronary heart disease; CV, coefficient of variation; CVD, cardiovascular disease; FG, fasting glucose; FSIGTT, frequently sampled intravenous glucose tolerance test; ICA, internal carotid artery; IGT, impaired glucose tolerance; IMT, intima-media thickness; IRAS, Insulin Resistance Atherosclerosis Study; NGT, normal glucose tolerance; OGTT, oral glucose tolerance test; PAI, plasminogen activator inhibitor; TG, triglycerides; WHO, World Health Organization.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Clinically recognized diabetes is an important risk factor for coronary heart disease (CHD) (1). However, despite numerous investigations, pooled analyses (2), and reviews (3–5), it is unclear whether nondiabetic hyperglycemia is associated with CHD. Contradictory results may have been due to the inclusion of people with undiagnosed diabetes (misclassification) and to failure to adjust for classical heart disease risk factors. However, even when investigators have used an oral glucose tolerance test (OGTT) to exclude people with diabetes, the relationship between glycemia and risk of heart disease is inconsistent. Barrett-Connor (3) recently reported on four large prospective studies with long-term follow-up. In two large prospective studies, the Helsinki Policemen Study and a study of London civil servants, an independent, increased risk of fatal CHD was reported (2.7 and 1.7, respectively) among people with impaired glucose tolerance (IGT). No independent effect of IGT on CHD risk was observed in the Paris Prospective Study or the Rancho Bernardo cohorts.

Another limitation of this area of research is its focus on CHD mortality. Few reports have examined the relationship between glycemia and the underlying disease process, atherosclerosis. Folsom et al. (6) reported a positive (but nonsignificant) relationship between fasting nondiabetic hyperglycemia and intima-media thickness (IMT) of the carotid artery, which is a measure of early atherosclerosis. In addition to this Atherosclerosis Risk in Communities (ARIC) report, which represents more than 14,000 participants in a population-based epidemiological cohort, two other studies have used the IMT measure of subclinical atherosclerosis in 21 and 71 subjects with IGT (7,8). One study observed greater IMT in people with IGT compared with those with normal glucose tolerance (NGT) (8); IMT did not differ between those with IGT and those with type 2 diabetes.

Data from the Insulin Resistance Atherosclerosis Study (IRAS) are particularly useful in addressing the question of CHD risk along the glycemia continuum because the sample was recruited to include large num-

bers of people with IGT, as defined by the World Health Organization (WHO), and people with clinically diagnosed diabetes. Moreover, all IRAS participants have a measure of subclinical atherosclerosis via ultrasonography of the carotid artery. The large number of minority participants in the cohort allows the findings to be generalized to multiple ethnic groups. We hypothesized that carotid IMT will increase with worsening glucose tolerance, from normoglycemia to IGT to diabetes.

Characterizing the risk of CHD in people with IGT will help to determine treatment and prevention strategies for those individuals. If the risk of atherosclerosis is similar in people with IGT and NGT, we might merely screen aggressively for diabetes, and then intensively treat glucose levels, to prevent CHD. Alternatively, if atherosclerosis is much greater in people with IGT than in those with NGT, primary prevention of IGT and diabetes would be more important for the prevention of CHD in diabetes.

RESEARCH DESIGN AND METHODS

— The IRAS is a multicenter epidemiological study exploring the relationships among levels of glucose and insulin, insulin resistance, cardiovascular disease (CVD) risk factors and risk behaviors, and clinical and subclinical CVD in a large multiethnic population. The study represents the first large attempt to directly measure both insulin resistance and subclinical atherosclerosis as well as numerous CVD risk factors. The study was approved by the institutional review committees of each participating center, and all subjects gave informed consent. The 1,625 men and women in the study were enrolled at four sites: San Antonio, Texas; San Luis Valley, Colorado; and Oakland and Los Angeles, California. Sampling was designed to identify potential participants of various ages (40–69 years), ethnicity (non-Hispanic white, Hispanic, and African-American), and glucose tolerance strata (normoglycemia, IGT, and type 2 diabetes). To meet the recruitment goals for glucose tolerance strata, the clinic staff oversampled from lists of people known to have IGT (as determined by OGTT) or moderately elevated fasting glucose (FG) levels. People with diabetes were also recruited. The use of insulin in the previous 5 years was an exclusion criterion. Recruitment strategies and results have been previously reported (9).

Participants attended two examinations, usually within a 2-week period. Age, sex, ethnicity, smoking status, and diabetes history and treatment were obtained by self-report. Total, LDL, and HDL cholesterol were measured in plasma using the beta-quantification method as described by the Lipid Research Clinics (10). Triglycerides (TG) were measured by enzymatic methods using glycerol-blanked assays on an autoanalyzer (Hitachi, Tokyo). Blind duplicate samples were prepared for 10% of the participant samples and were submitted to the laboratories as part of an external quality control program. The externally measured coefficient of variation (CV) was 4% each for LDL cholesterol, HDL cholesterol, and TG. Insulin sensitivity was assessed by the frequently sampled intravenous glucose tolerance test (FSIGTT) with minimal model analysis (11,12). Plasminogen activator inhibitor (PAI)-1 was measured by enzyme-linked immunosorbent assay (13); its external CV was 14%.

A 75-g OGTT was administered to all participants; fasting and 2-h postload blood samples were collected. Plasma glucose was measured using the glucose oxidase technique on an autoanalyzer (Yellow Springs Instruments, Yellow Springs, OH); the CV was 3%. IGT and diabetes were defined according to WHO criteria (14). IGT was defined as FG $<$140 mg/dl and 2-h glucose $\geq$140 and $<$200 mg/dl. Diabetes was defined as FG $\geq$140 mg/dl or 2-h glucose $\geq$200 mg/dl. Participants whose OGTT results met the above criteria for diabetes but who did not report a previous diagnosis of diabetes were considered to have new diabetes. Those whose OGTT results met the above criteria for diabetes and who reported a previous diagnosis of diabetes were considered to have established diabetes. Participants taking oral hypoglycemic medications were considered to have established diabetes, regardless of their OGTT results or their report of a previous diagnosis. NGT was defined as FG and 2-h glucose $<$140 mg/dl.

Anthropometric measures were made following a standardized protocol (15); BMI was calculated as weight in kilograms divided by the square of height in meters. Sitting blood pressure was measured after a 5-min rest; the average of the second and third measurements was computed. Hypertension was defined as systolic blood pressure $>$140 mg/dl, diastolic blood pressure $>$90 mg/dl, or the current use of antihypertensive medication.

High-resolution B-mode carotid ultrasonography was performed to provide an index of atherosclerosis (16). The scanning and reading protocol was identical to that used in the Cardiovascular Health Study (17). A bilateral assessment of the wall thickness was made in the internal carotid artery (ICA) and the common carotid artery (CCA). For the ICA, the sonographer sought the site of maximal IMT 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). For the CCA, bilateral images were obtained 1 cm proximal to the dilatation of the carotid bulb at a single (lateral) angle.

Ultrasound images were recorded on super-VHS tape and sent weekly to a central reading facility. One reader at this facility was responsible for reading all ultrasound images from the IRAS. For each of the eight available images, the maximal IMT was obtained over a 1-cm segment of the far arterial wall (distant from the skin surface). (Because of the geometry of the artery and the physics of ultrasound assessment, measurements of the far wall are considered to have greater reliability and validity [18] and are the focus of these analyses). Two summary measures were calculated: *1*) the mean of the six ICA sites and *2*) the mean of the two CCA sites. To allow equal weighting of the left and right arteries in the presence of missing data (on average, 6.5 and 0.6% at each ICA at CCA site, respectively), the mean values of the available measurements on the left ICA and the mean values of the available measurements on the right ICA were calculated, and then the mean of these two means was used in analysis.

A subset of 43 participants were rescanned for an assessment of intrasonographer variability; Pearson's correlation coefficient between scans was 0.86 and 0.75 for the CCA-IMT and ICA-IMT, respectively. Likewise, 64 scans were reread to assess intrareader variability; the correlation coefficient between scans was 0.95 and 0.94 for the CCA-IMT and ICA-IMT, respectively.

Statistical methods

The primary independent variable of interest was the four-level glucose tolerance variable (WHO-defined NGT, IGT, new diabetes, or established diabetes). We divided the persons with diabetes into two groups based on our previous findings in this cohort of differing risk factor profiles between these

Table 1—*Descriptive statistics for categories of glucose tolerance*

	NGT	IGT	New diabetes	Established diabetes
*n**	635	313	172	272
Men (%)	48	40	42	48
Ethnicity (%)				
White	41	39	35	36
African-American	26	28	37	29
Hispanic	33	33	28	35
Clinical center (%)				
San Antonio	25	27	24	17
San Luis Valley	28	22	13	34
Oakland	21	21	38	18
Los Angeles	25	30	26	32
Age (years)	53.7 ± 8.5	57.0 ± 7.7	57.7 ± 8.2	56.8 ± 8.2
Smoking status (%)				
Current	16	16	18	16
Past	39	38	40	45
Never	45	46	42	39
Hypertension (%)	27	42	56	50
BMI (kg/m^2)	27.4 ± 4.9	30.3 ± 6.3	31.9 ± 5.7	30.9 ± 5.9
LDL cholesterol (mmol/l)	3.62 ± 0.91	3.72 ± 0.96	3.75 ± 0.96	3.59 ± 0.88
HDL cholesterol (mmol/l)	1.24 ± 0.41	1.16 ± 0.39	1.11 ± 0.31	1.01 ± 0.28
TG (mmol/l)	1.40 ± 0.93	1.78 ± 1.06	1.95 ± 1.31	2.20 ± 2.05
FG (mmol/l)	5.2 ± 0.6	5.7 ± 0.6	7.8 ± 2.6	10.3 ± 3.1
2-h glucose (mmol/l)	5.9 ± 1.2	9.1 ± 0.9	14.7 ± 3.3	18.8 ± 4.9
Insulin sensitivity ($10^{-4} \cdot min^{-1} \cdot \mu U^{-1} \cdot ml^{-1}$)	2.6 ± 2.1	1.3 ± 1.2	0.6 ± 0.8	0.6 ± 0.8
PAI-1 (ng/ml)	20 ± 20	26 ± 21	32 ± 21	32 ± 25
ICA-IMT (μm)	823 ± 344	876 ± 362	903 ± 395	984 ± 472
CCA-IMT (μm)	777 ± 188	827 ± 205	858 ± 210	890 ± 274

Data are *n*, %, or means ± SD. *Sample sizes differ by no more than 14 for NGT, 13 for IGT, 10 for new diabetes, 11 for established diabetes.

groups (19). We examined two dependent variables: IMT of the ICA and the CCA. Descriptive data are presented for each category of glucose tolerance (Table 1). We modeled the relationship between WHO glucose tolerance category and IMT using the analysis of covariance technique. In model 1, we adjusted for possible confounding variables, including age, sex, ethnicity, clinical center, and smoking status. In model 2, in addition to the variables in model 1, we adjusted for hypertension, BMI, insulin sensitivity, LDL and HDL cholesterol, TG, and PAI-1, all possible mediators of the glucose tolerance–atherosclerosis relationship. Of the total 1,625 participants in the IRAS, 233 were excluded from these analyses because of missing data points for either IMT measures or insulin sensitivity (9).

Interactions of glucose tolerance category and sex and of glucose tolerance category and ethnicity were considered. Based on previous CHD incidence and mortality data, we hypothesized that women with diabetes would have greater increases in wall thickness than women without diabetes (1) and that whites with diabetes would have greater increases relative to either African-Americans (20–22) or Hispanics (22,23). The glucose tolerance category–ethnicity interaction reached statistical significance for the ICA ($P = 0.006$), but not for the CCA ($P = 0.37$). Furthermore, because ethnicity is partially confounded by clinical center in the IRAS (Hispanics were sampled in San Antonio and San Luis Valley only, and African-Americans were sampled in Oakland and Los Angeles only), we examined the ethnic groups (and the interaction) separately by geographic region, as we had done previously in the IRAS (24,25). In this case, a significant glucose tolerance category–ethnicity interaction persisted for the ICA ($P = 0.03$) for the pooled California clinics (African-Americans versus whites), but not for the pooled San Antonio and San Luis Valley clinics (Hispanics versus whites). Thus, for the ICA, data are presented by geographic region. The glucose tolerance category–sex interaction did not reach statistical significance ($P > 0.15$).

Finally, Spearman's correlation coefficients were obtained to describe the relationship between FG (an average of two values collected at a 2-week interval) and IMT.

RESULTS — There was a general trend toward worsening atherosclerotic risk factor profiles with worsening glucose tolerance (Table 1). In particular, hyperlipidemia, hypertension, insulin resistance, and abnormal clotting factors were observed among subjects with IGT, and most often in persons with diabetes. However, hypertension, increased LDL, and increased BMI were less prevalent among subjects with established diabetes than among those with new diabetes. Subjects with established diabetes were also more likely to be ex-smokers. On average, people with established diabetes reported having diabetes for 7 years (SD = 7). A stepwise increase in ICA-IMT and CCA-IMT was observed across glucose tolerance categories.

Adjusted for demographic variables and smoking (model 1), CCA-IMT increased slightly across glucose tolerance categories with the largest increase in wall thickness observed between subjects with new diabetes and those with established diabetes (802, 822, 831, and 896 μm for NGT, IGT, new diabetes, and established diabetes, respectively) ($P < 0.0001$ for trend) (Fig. 1). Pairwise comparisons indicated that people with established diabetes had significantly greater wall thickness than those in each of the other groups ($P < 0.001$). However, no significant differences were found among the other groups (NGT, IGT, and new diabetes). The trend was attenuated further when adjusting for other CVD risk factors (819, 827, 826, and 891 μm), although *P* values for trend and pairwise comparison were not materially affected.

When we examined the San Antonio and San Luis Valley IRAS clinic data, we found a steeper pattern of increase in the ICA-IMT across glucose tolerance groups (Fig. 2). Adjusted for demographic characteristics and smoking (model 1), ICA-IMT was 823, 801, 917, and 994 μm for NGT, IGT, new diabetes, and established diabetes, respectively ($P < 0.0001$ for trend). Significant differences ($P < 0.05$) were

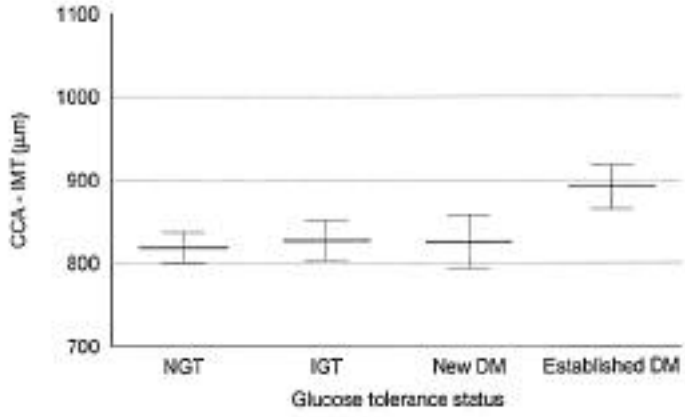

Figure 1—*CCA-IMT and glucose tolerance status data, adjusted for demographic factors and CVD risk factors (model 2). Bars represent 95% CIs of the point estimate. DM, diabetes mellitus.*

observed between IGT and new diabetes subjects, IGT and established diabetes subjects, and NGT and established diabetes subjects. ICA-IMT did not differ between subjects with NGT and those with IGT. Again, the trend was attenuated when adjustment was made for other CVD risk factors (849, 805, 899, and 981 µm). No difference was noted between NGT and IGT participants, nor between IGT and new diabetes participants.

When we examined the clinic data from the two California IRAS sites, we observed a different relationship between glucose tolerance and ICA-IMT for the two ethnic groups, as noted previously. Among African-Americans, the relationship was generally flat: ICA-IMT, adjusted for demographic characteristics and smoking, was 930, 895, 859, and 947 µm for NGT, IGT, new diabetes, and established diabetes, respectively. No significant pairwise differences were noted. Among whites, subjects with IGT had the greatest IMT, which was significantly greater than that found in NGT subjects: ICA-IMT was 867, 1025, 981, and 966 µm for subjects NGT, IGT, new diabetes, and established diabetes, respectively. No other pairwise differences were noted. These findings were affected little by further adjustment for CVD risk factors.

The correlations between average FG and IMT were 0.25 and 0.20 for the CCA and ICA, respectively ($P < 0.0001$). Correlations were slightly lower for 2-h glucose ($r = 0.19$). These correlations are larger than those observed between LDL cholesterol and IMT (0.15 and 0.12 for CCA and ICA, respectively; $P < 0.0001$).

CONCLUSIONS

— The strengths of this study are its tri-racial composition, its ample numbers of subjects with IGT and diabetes, and its direct measure of subclinical atherosclerosis. B-mode ultrasonography is a valid and reliable tool for the measurement of subclinical atherosclerosis in population studies. IMT measured using this noninvasive technique has been validated against histological specimens of the carotid artery (16,18,26). IMT is associated with risk factors for coronary atherosclerosis (27,28). The measure correlates with direct indicators of coronary artery disease, specifically those assessed by coronary angiography (29,30). It is important as a significant, independent predictor of new CHD events, as shown in two studies of 2- and 5-year follow-up periods (31,32). Finally, interventions that slow IMT progression, such as lipid lowering, result in concomitant reductions in CVD events (33) and in progression of coronary atherosclerosis (34). The reproducibility of the highly standardized scanning and reading protocols is good in this study and other studies (35), with correlation coefficients of ~0.8 or greater for repeat studies. In summary, ultrasonographically measured IMT of the carotid artery is a valid indicator of coronary atherosclerosis.

As hypothesized, IMT generally increased across the categories of worsening glucose tolerance. Adjustment for demographic characteristics and smoking minimized the relationship in the CCA, with the most pronounced increase in wall thickness observed at the level of established diabetes. Participants with established diabetes exhibited considerably larger IMT (by 70 µm) despite reduced levels of a number of important risk factors (e.g., LDL cholesterol and hypertension). The ICA-IMT showed a steeper relationship than the CCA-IMT to worsening glucose tolerance, especially among subjects with new and established diabetes (San Luis Valley and San Antonio sites). Specifically, the subjects with new diabetes exhibited an ICA-IMT that was 100 µm thicker than that of the NGT subjects, and the ICA-IMT of subjects with established diabetes was ~150 µm thicker than that of the NGT subjects. Folsom et al. (6) have reported greater wall thickness in people with diabetes compared with those without diabetes (70 µm). As in the IRAS, adjustment for hypertension and plasma lipids reduced this effect only slightly. This statistical technique may be considered an "overadjustment" because it adjusts for factors that may mediate the glycemia-atherosclerosis relationship. LDL cholesterol, in particular, is an important risk factor for increased carotid IMT, and it is adversely elevated in people with diabetes. However, only a marginal attenuation of the effect was observed with adjustment by this factor and

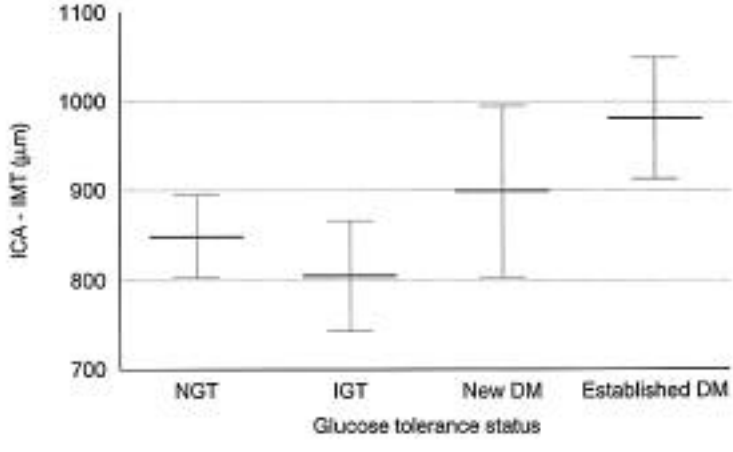

Figure 2—*ICA-IMT and glucose tolerance status data from the San Antonio and San Luis Valley IRAS clinics only (see STATISTICAL METHODS for details), adjusted for demographic factors and CVD risk factors (model 2). Bars represent 95% CIs of the point estimate. DM, diabetes mellitus.*

other factors, suggesting that other metabolic abnormalities, and possibly glycemia itself, are responsible for this increased risk.

We have previously reported that duration of established diabetes is not associated with IMT in this cohort (19). While this is consistent with many other reports assessing duration of diabetes and CHD risk, we (as well as others) caution that self-reported duration of diabetes is imprecise because of a variable and sometimes long prodromal period. Nevertheless, these IRAS data suggest that the absolute level of glycemia consistent with overt diabetes, and not the duration of diabetes, may be the more important risk factor. Also, we have reported that in the IRAS cohort, insulin resistance is associated with increased carotid IMT in Hispanic and non-Hispanic whites but not in blacks (36). The association is partially mediated by traditional CVD risk factors and is stronger in the ICA than in the CCA.

Participants with IGT did not exhibit levels of wall thickness higher than those of the NGT participants in this study (except for the isolated finding among whites in the California IRAS clinics). In the ARIC cohort (6), subjects with elevated FG had nonsignificantly elevated levels of wall thickness (20 μm) compared with NGT subjects. Similarly, Niskanen et al. (7) reported only modestly (nonsignificantly) increased IMT in 21 subjects with IGT compared with NGT subjects. The unadjusted IRAS data show similar intermediate levels of wall thickness for the CCA among IGT subjects; these levels are minimized by adjustment for risk factors. One explanation for this weak association is the misclassification of people with IGT through use of the WHO criteria. It is well known that IGT, as defined, is a transient state. A large proportion of people found to have IGT on a single OGTT are classified in the NGT range on a repeat test (37). When the classification is disregarded and the relationship across the range of FG is examined, a moderate correlation of 0.20 to 0.25 is observed, indicating the importance of using actual glucose values rather than a classification system.

Different relationships between glucose tolerance category and wall thickness based on ethnicity were hypothesized. However, we observed a difference in only one segment of the artery (the ICA) and only between white and African-American participants in the California IRAS clinics. The relationship was not consistent with our hypothesis, stated above, that diabetes is a more potent risk factor for whites than for African-Americans or Hispanics. Furthermore, the lack of a similar interaction in the other carotid segment (the CCA) leads us to conclude that the interaction in the ICA could be a chance finding or a result of measurement error. (Reproducible measurements are more difficult to obtain in the ICA because of the complex arterial geometry).

Although many studies have reported a relatively greater increase in the risk of clinical CHD in diabetic women than in diabetic men, this pattern was not observed with the use of our subclinical measure of atherosclerosis. Folsom et al. (6) did not observe this difference in the ARIC cohort either. Orchard (38) suggests that the excess cardiovascular risk suffered by women is more closely associated with mortality from heart disease rather than an increased incidence of heart disease or atherosclerosis. These findings raise the possibility that the sex differential is related not to the extent of atherosclerosis but to a thrombotic component leading to the clinical CHD event.

The ICA appeared to be more susceptible than the CCA to increased thickening, particularly in subjects with new and established diabetes in the San Antonio and San Luis Valley IRAS clinics. This segment of the carotid artery is more susceptible to early atherosclerosis than the CCA (39). It is more often the site of focal atherosclerotic lesions linked to lipid accumulation and thrombotic events, whereas in the CCA, atherosclerosis is manifested by diffuse thickening (39). These IRAS data suggest that chronic hyperglycemia may have a greater effect on the ICA. Furthermore, in another epidemiological cohort, the ICA-IMT was more strongly associated with risk factors for atherosclerosis and existing CHD and atherosclerotic disease than was the CCA-IMT (40). Consequently, the greatly increased IMT observed in the ICA of IRAS participants with diabetes may portend a greater risk of CHD.

Consistent with reports on increased risk of cardiovascular events and mortality in people with established diabetes, the IRAS data show considerably increased carotid IMT among people with established diabetes. This increase was observed despite improved CHD risk factor profiles in the established diabetic subjects (undoubtedly due to treatment with oral hypoglycemic agents or to behavioral changes) and in the absence of diabetic subjects using insulin, who were excluded from the IRAS. Both conditions likely truncated the mean IMT measure among participants with established diabetes, resulting in a more conservative estimate of the overall association of hyperglycemia with atherosclerosis. People with undiagnosed diabetes also have increased carotid IMT, particularly in the ICA, the carotid segment related to early atherosclerosis. These effects are not explained by traditional CVD risk factors, which are more common in people with diabetes. One possible explanation for increased atherosclerosis is an interaction of glycemia with traditional risk factors. Work in animal models indicates an interaction of hyperglycemia with hyperlipidemia in accelerating atherosclerosis (41). Alternatively, other unmeasured factors, such as oxidative modification of LDL cholesterol (42,43) or glycation of lipoproteins (44,45), may be operating.

Finally, we did not observe increased levels of IMT among participants with IGT as we had hypothesized. These individuals have atherogenic risk factor profiles (and in some studies have an increased risk of CHD), yet they do not yet exhibit substantially increased subclinical disease in this study or in other studies. However, for a number of reasons, we should not overlook the IGT state as a time to begin intervention. First, we and others have noted an increased prevalence of abnormal CHD risk factors, including hyperlipidemia and hypertension, associated with the IGT state. Prevention and treatment of these factors are known to reduce subsequent CHD risk. Furthermore, because IGT is a precursor of type 2 diabetes (46,47) and type 2 diabetes has an associated two- to fourfold risk of CHD, the prevention and treatment of IGT may ultimately reduce the risk of diabetes-associated CHD. Finally, we observed a trend (although a nonsignificant one) toward increasing CCA-IMT with IGT in the IRAS. This finding should be considered in the context of recent evidence of a graded relationship between carotid IMT and CHD incidence (32), suggesting that even small increases in IMT are associated with increases in CHD risk.

In summary, these data indicate that the onset of overt diabetes accelerates the development of atherosclerosis. Increased IMT was not observed among people with IGT, although their CHD risk factor profile had begun to deteriorate. These results are important because they help focus prevention programs on the most effective times for intervention. To prevent CHD in diabetes, we should aggressively screen for

diabetes and then intensively treat glucose levels and other concomitant risk factors (48). The IGT state may also be an important time for intervention. However, the approach to intervention is unclear until a more accurate diagnostic test is found and definitive guidelines for treatment are available from clinical trials.

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