The Relationship Between Dysglycemia and Atherosclerosis in South Asian, Chinese, and European Individuals in Canada

A randomly sampled cross-sectional study

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OBJECTIVE — Raised glucose levels extending from normal into the diabetic range (dysglycemia) are an emerging risk factor for clinical cardiovascular events. The relationship between dysglycemia and atherosclerosis (AS) in the general population and in different ethnic groups remains controversial.

RESEARCH DESIGN AND METHODS — Glucose tolerance, HbA_{1c}, other metabolic risk factors for AS, and carotid mean maximal intimal media thickness were assessed in a random sample of 979 Canadians of South Asian, Chinese, and European descent.

RESULTS — The age and sex-adjusted intimal medial thickness increased 0.026 mm for every 0.9% increase in HbA_{1c} in all participants ($P < 0.0001$) and in those of South Asian ($P = 0.018$), Chinese ($P = 0.002$), and European ($P < 0.0001$) descent. This progressive curvilinear relationship was most apparent at HbA_{1c} levels >5.7%. The HbA_{1c}-AS relationship persisted after adjustment for ethnicity, age, sex, diabetes status, abdominal obesity, insulin resistance, insulin secretion, fasting free fatty acids, blood pressure, and/or dyslipidemia ($P < 0.004$). Both diabetes ($P = 0.002$) and HbA_{1c} ($P < 0.0001$) were determinants of the intimal medial thickness when included in separate statistical models. When included together in a single model, HbA_{1c} ($P < 0.0001$) but not diabetes ($P = 0.6$) was a significant determinant.

CONCLUSIONS — The degree of AS is related to the level of HbA_{1c} irrespective of diabetes status and independent of abdominal obesity and other markers of the metabolic syndrome. This progressive relationship between HbA_{1c} and AS was observed within different ethnic groups.

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People with diabetes are at high risk for cardiovascular (CV) disease (1). This risk varies with glucose levels as well as HbA_{1c} levels. This graded relationship between plasma glucose and CV risk is observed in people with diabetes (2–4) and in nondiabetic individuals with high glucose levels that are below the diabetes cutoffs (5–10).

These data suggest that glucose may promote atherosclerosis (AS) either directly or indirectly. Alternatively, it may be a marker for metabolic abnormalities that may themselves promote AS. To date, few studies have explored this link between dysglycemia (i.e., any elevated glucose level) and AS using standardized methods. In addition, this relationship has not been explored within different ethnic groups.

The Study of Health Assessment and Risk in Ethnic Groups (SHARE) measured diabetes prevalence, glucose intolerance, HbA_{1c}, other CV risk factors, and carotid AS (by B-mode carotid ultrasound) in a large population-based sample of Canadians of South Asian, Chinese, and European origin (11). This article reports on the importance of dysglycemia as an AS risk factor and explores the relationship between ethnicity, metabolic CV risk factors, and AS in this population.

RESEARCH DESIGN AND METHODS

Study population

SHARE was a population-based study of carotid AS and its determinants in 985 individuals of South Asian, Chinese, and European origin living in Canada for ≥5 years. Detailed descriptions of the protocol, sampling frames, and major results have been published (11,12). Briefly, a database of South Asian and Chinese surnames in the telephone directories of Hamilton, Toronto, and Edmonton, Canada, was randomly sampled. Selected households were mailed an introductory letter and then contacted by phone. Eligible individuals of the appropriate ethnicity (defined by their ancestral origins) aged 35–75 years who had lived in Can-

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Abbreviations: AS, atherosclerosis; CV, cardiovascular; HOMA, homeostasis model assessment; HOMA-β, HOMA for β-cell secretion; HOMA-IR, HOMA for insulin resistance; IMT, intimal media thickness; MMIMT, maximum IMT; SHARE, Study of Health Assessment and Risk in Ethnic Groups.

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

Table 1—*Relationship between glucose tolerance and related cardiovascular risk factors*

	NGT	IGT	New diabetes	Old diabetes	*P*
n	734 (75.0)	142 (14.5)	66 (6.7)	37 (3.8)	N/A
Ethnicity	—	—	—	—	0.0002
South Asian	229 (67.4)	59 (17.4)	32 (9.4)	20 (5.9)	0.0004*
Chinese	246 (78.1)	47 (14.9)	14 (4.4)	8 (2.5)	0.07†
European	259 (79.9)	36 (11.1)	20 (6.2)	9 (2.8)	0.0005‡
Age	48.1 ± 9.5	51.4 ± 9.7	56.0 ± 10.3	58.2 ± 9.3	<0.0001
Male subjects	360 (49.1)	67 (47.2)	29 (43.9)	18 (48.7)	0.54
Treated hypertension§	67 (9.2)	29 (20.4)	18 (27.3)	17 (46)	<0.0001
Treated hyperlipidemia§	34 (4.6)	12 (8.5)	6 (9.1)	7 (18.9)	0.02
BMI (kg/m^2)§	25.5 ± 4.3	26.8 ± 4.3	27.9 ± 4.3	27.4 ± 4.3	<0.0001
Waist-to-hip ratio§	0.86 ± 0.07	0.88 ± 0.07	0.92 ± 0.07	0.92 ± 0.07	<0.0001
Systolic pressure (mmHg)§	116.7 ± 15.5	121.9 ± 15.4	127.2 ± 15.6	126.8 ± 15.6	<0.0001
Diastolic pressure (mmHg)§	73.6 ± 10.5	76.4 ± 10.4	80.7 ± 10.6	78.8 ± 10.6	<0.0001
Triglycerides (mmol/l)§	1.60 ± 1.22	2.16 ± 1.22	2.76 ± 1.23	2.55 ± 1.23	<0.0001
HDL cholesterol (mmol/l)§	1.18 ± 0.32	1.07 ± 0.320	1.01 ± 0.33	0.90 ± 0.33	<0.0001
LDL cholesterol (mmol/l)§	3.19 ± 0.79	3.31 ± 0.79	3.21 ± 0.80	2.98 ± 0.79	0.71
Total cholesterol (mmol/l)§	5.09 ± 0.92	5.30 ± 0.91	5.32 ± 0.92	4.97 ± 0.92	0.16
Free fatty acids (mg/l)§	483 ± 210	594 ± 208	667 ± 211	725 ± 211	<0.0001
Fasting insulin (pmol/l)§	73.8 ± 52.3	92.8 ± 51.9	131.4 ± 52.6	162.4 ± 52.6	<0.0001
HOMA-IR (mU · mmol/l^2)§	2.33 ± 2.5	3.16 ± 2.5	6.51 ± 2.5	9.81 ± 2.5	<0.0001
HOMA-β (mU/mmol)§	138.5 ± 70.5	141.8 ± 70.1	108.1 ± 71.0	91.5 ± 71.0	<0.0001

Data for continuous variables are means ± 1 SD; data for count variables are *N* (%). **P* for distribution across glucose tolerance status vs. Chinese; †*P* for distribution vs. Europeans; ‡*P* for distribution vs. South Asians; §age and sex adjusted rates and values. IGT, impaired glucose tolerance; NGT, normal glucose tolerance.

ada for ≥5 years were invited for assessment. Once a South Asian or Chinese participant agreed to attend, a European household was randomly sampled from all of the other surnames within the same geographic postal code. The results in 979 people in whom glucose tolerance status could be determined are reported here.

Biochemical measurements

After providing written informed consent, participants had a detailed clinical assessment and provided urine and fasting blood samples. Individuals with no history of diabetes also had an oral glucose tolerance test. All assays were performed centrally without any clinical information. Glucose and lipids were measured as previously described (11). HbA_{1c} was measured by low-pressure cation exchange chromatography on a Ciba Corning 765 Glycomat analyzer and a Glucamal reagent kit (Drew Scientific, London, U.K.). Insulin was measured by a highly specific radioimmunoassay, with cross-reactivity with only proinsulin of ~40% at mid-curve (Coat A Count; Diagnostic Products, Los Angeles, CA). Free fatty acids were measured by an assay that detects fatty acids of 6–20 carbon lengths (NEFA C; Wako Chemical, Richmond, VA). The arithmetic approximation to the homeostasis model assessment (HOMA) for β-cell secretion (HOMA-β) and for insulin resistance (HOMA-IR) were calculated from the fasting plasma glucose and insulin levels as follows (13): HOMA-β = (20 × fasting insulin [mU/l])/(fasting plasma glucose [mmol/l] − 3.5) and HOMA-IR = (fasting insulin [mU/l]) × (fasting plasma glucose [mmol/l]/22.5).

Carotid ultrasound measurements

All participants underwent carotid B-mode ultrasonography as previously described (11). The mean of the maximum intimal media thickness (MMIMT) was calculated by averaging the segment maximum IMT measurements from the far and near walls of the left and right common, bifurcation, and internal carotid artery segments. All scans and off-line measurements were performed by sonographers blinded to the participants' other data.

Statistical analyses

All analyses were performed with SAS (Version 6.12) and (unless indicated otherwise) were age- and sex-adjusted to the whole SHARE population. χ^2 testing was used to compare proportions; ANCOVA was used to analyze continuous variables, and the Tukey-Kramer test was used for pairwise comparisons. Logistic regression and multiple regression models were used to assess independent determinants of abnormal glucose categories and MMIMT, respectively. HbA_{1c} deciles were used to divide the study groups, and the mean HbA_{1c} within each decile (for all participants) was plotted against the adjusted MMIMT.

RESULTS

Participants

Data were collected from 979 of the 985 South Asian (*n* = 340, 45% female), Chinese (*n* = 315, 49% female), and European (*n* = 324, 52% female) participants who either completed a glucose tolerance test or had a diabetes history. There were no differences in sex. However, European participants (mean age 51.3 years) were significantly older than South Asian (mean age 49.4 years, *P* for comparison = 0.01) and Chinese participants (mean age 47.8 years, *P* for comparison <0.0001), and South Asian participants were significantly older than Chinese participants (*P* = 0.04). Age- and sex-adjusted

Table 2—*Multivariate relationship between risk factors and any abnormal glucose category

Independent variables	Dependent variable: impaired glucose tolerance, impaired fasting glucose, or diabetes	
	Odds ratio (95% CI)	*P*
Age (per 10 years)	1.65 (1.29–2.12)	<0.0001
Male sex	0.63 (0.36–1.10)	0.1
Ethnicity		0.01
South Asian vs. European	1.25 (0.73–2.15)	0.4
South Asian vs. Chinese	2.30 (1.33–3.97)	0.003
Chinese vs. European	0.54 (0.28–1.06)	0.07
Hypertension on therapy	0.93 (0.53–1.62)	0.8
Hyperlipidemic on therapy	1.52 (0.74–3.13)	0.3
BMI (per 4.4 kg/m^2)	0.84 (0.64–1.10)	0.2
Waist-to-hip ratio (per 0.09)	1.51 (1.13–2.03)	0.005
Systolic BP (per 18 mm)	1.22 (0.92–1.63)	0.2
Diastolic BP (per 12 mm)	1.23 (0.91–1.66)	0.2
Ln triglyceride (per 0.57 mmol/l)	1.50 (1.16–1.94)	0.002
Total cholesterol (per 0.94 mmol/l)	0.89 (0.71–1.11)	0.3
Ln fasting FFA (per 0.46 mg/l)	1.47 (1.14–1.89)	0.0027

*Impaired glucose tolerance, impaired fasting glucose, or diabetes. All estimates are adjusted for the variables listed above as well as natural logarithm fasting insulin levels. BP, blood pressure; FFA, free fatty acid; Ln, natural logarithm.

MMIMT values for these three groups have been reported previously (11).

Relationship between glucose tolerance status and other metabolic CV risk factors

Individuals with higher degrees of glucose intolerance were older and more likely to be of South Asian ethnicity than individuals with normal glucose tolerance (Table 1). Indeed, the age- and sex-adjusted HbA_{1c} levels (± SD) in the subjects of South Asian, Chinese, and European ethnicity were 5.90 ± 0.86, 5.63 ± 0.87, and 5.43 ± 0.86%, respectively ($F = 29.13$ and $P < 0.0001$ for differences among all three groups; $P = 0.0003$ for South Asian vs. Chinese; $P < 0.0001$ for South Asian vs. European; and $P = 0.077$ for Chinese vs. European). After adjusting for age and sex, individuals with higher degrees of glucose intolerance were also more likely to have a history of treated hypertension ($P < 0.0001$); a history of hyperlipidemia ($P = 0.02$); higher blood pressure, BMI, waist-to-hip ratio, fasting insulin, estimated insulin resistance, free fatty acids, and triglycerides; and lower HDL cholesterol and estimated β-cell function ($P < 0.0001$ for all) (Table 1).

When these risk factors were analyzed in a multivariate model (Table 2), the independent determinants of any abnormal glucose category (i.e., either impaired fasting glucose, impaired glucose tolerance, or diabetes) were ethnicity (specifically the South Asian compared with the Chinese group), age, waist-to-hip ratio, and the natural logarithm of triglycerides and fasting free fatty acids. Insulin secretion and insulin resistance (by HOMA) were highly correlated with each other and with insulin levels; when tested in separate models that included the other variables in Table 2, they were also strong independent determinants of any abnormal glucose category ($P < 0.0001$) (Table 3).

Relationship between HbA_{1c}, glucose, other metabolic CV risk factors, and AS

The relationship between metabolic CV risk factors and AS was explored by analyzing the relationship between ambient glycemia (i.e., HbA_{1c}), determinants of abnormal glucose tolerance, and MMIMT. After age and sex adjustment (Table 4), significant determinants of MMIMT included HbA_{1c} and fasting plasma glucose ($P < 0.0001$ for both), HOMA-β ($P = 0.001$), BMI ($P = 0.03$), and systolic blood pressure ($P < 0.0001$). MMIMT was not associated with postload glucose, HOMA-IR, any lipid abnormality, fasting free fatty acids, fasting insulin, abdominal obesity, or diastolic blood pressure (Table 4).

Further analyses focused on the relationship between HbA_{1c} and the carotid MMIMT. First, the whole study population was divided into 10 equally sized groups by HbA_{1c} decile. As shown in Fig. 1*A*, there was a progressive curvilinear relationship between age- and sex-adjusted MMIMT and HbA_{1c}. Although this relationship was most apparent as the HbA_{1c} level rose above 5.7%, no threshold was detectable using a nonlinear statistical analysis. Second, a similar statistically significant relationship was noted when participants of South Asian ($P = 0.018$), Chinese ($P = 0.002$), and European ($P < 0.0001$) descent were analyzed separately using multiple regression techniques (Fig. 1*B*). Moreover, the strong significant relationship between HbA_{1c} and MMIMT persisted after adjusting for ethnicity in the multiple regression analysis ($P < 0.0001$) (Table 5), with no evidence of any heterogeneity between ethnicities (P for interaction between HbA_{1c} and ethnicity = 0.07). Third, several other re-

Table 3—*Multivariate relationship between measures of both insulin resistance and β-cell function and any abnormal glucose category*

Independent variable	Dependent variable: impaired glucose tolerance, impaired fasting glucose, or diabetes	
	Odds ratio (95% CI)	*P*
Ln fasting insulin (per 0.55 mmol/l rise)	2.14 (1.59–2.87)	<0.0001
Ln HOMA-β (per 0.66 rise)	0.26 (0.20–0.35)	<0.0001
Ln HOMA-IR (per 0.52 rise)	6.03 (4.13–8.80)	<0.0001

Estimates of the odds ratios for the independent variables in each row were determined in separate logistic regression models and were adjusted for all of the variables in Table 2. Ln, natural logarithm.

Table 4—*Univariate relationship between MMIMT and metabolic cardiovascular risk factors*

Variable	β	*P*	MMIMT (mm) rise/1 SD of the variable (95% CI)*	Variable's SD
HbA_{1c}	0.0287	<0.0001	0.026 (0.0159–0.0362)	0.91
FPG	0.0206	<0.0001	0.030 (0.0199–0.040)	1.5
BMI	0.003	0.03	0.011 (0.001–0.021)	4.4
Waist-to-hip ratio	0.1082	0.1	0.010 (−0.003 to 0.023)	0.09
Systolic BP	0.002	<0.0001	0.034 (0.023–0.045)	18
Diastolic BP	<0.001	0.1	0.009 (−0.002 to 0.020)	12
Ln HOMA-β	−0.032	0.001	−0.017 (−0.027 to −0.007)	0.66
Ln HOMA-IR	0.012	0.1	0.008 (−0.002 to 0.018)	0.52

All data are age and sex adjusted. Other variables tested for which the *P* value exceeded 0.1 were 2-h plasma glucose, total cholesterol, HDL cholesterol, LDL cholesterol, non-HDL cholesterol, and the natural logarithms of fasting triglyceride, fasting insulin, and fasting free fatty acids. *Increase in MMIMT per 1 SD change in the measured variable. BP, blood pressure; FPG, fasting plasma glucose; Ln, natural logarithm.

gression models were tested to determine whether the HbA_{1c} relationship could be explained by confounding with related variables. As noted in Table 5, a strong and robust relationship between MMIMT and HbA_{1c} was noted in different models that adjusted for diabetes status, abdominal obesity, insulin resistance, insulin secretion, fasting free fatty acids and/or dyslipidemia ($P < 0.004$ for all models).

Finally, to determine the relative importance of any diabetes (i.e., either new or established) versus HbA_{1c} as a determinant of AS, both of these variables were assessed separately and then together in the same regression model. After adjustment for age, sex, and ethnicity, both diabetes ($P = 0.002$) and HbA_{1c} ($P < 0.0001$) were significant determinants of MMIMT when they were included in separate models. However, when they were included together in the same model, HbA_{1c} ($P < 0.0001$) but not diabetes ($P = 0.6$) was a significant determinant of MMIMT (Fig. 2). This finding was confirmed when the analysis was repeated in the subset of individuals without evidence of diabetes; as in the overall group, HbA_{1c} remained an independent determinant of MMIMT after adjustment for age, sex, and ethnicity ($P = 0.029$).

CONCLUSIONS — These data show that the degree of glycemia as measured by HbA_{1c} is a strong independent determinant of AS. They demonstrate that the relationship between HbA_{1c} and AS is similar in different ethnic groups and cannot be accounted for by differences in abdominal obesity, dyslipidemia, free fatty acids, insulin secretion, or insulin resistance. The fact that the HbA_{1c}-AS relationship exists after controlling for the presence of diabetes, and the fact that there is no relationship between diabetes and MMIMT after controlling for HbA_{1c} (Fig. 2), suggests that the relationship between diabetes and AS is accounted for by the relationship between glucose levels and AS, and not by the presence or absence of diabetes per se.

These data also confirm that diabetes and glucose intolerance are strongly associated with other risk factors for CV disease, including age, abdominal obesity, hypertriglyceridemia, high free fatty acids, reduced insulin secretion, and increased insulin resistance. Furthermore, they confirm that *1*) the prevalence of diabetes and glucose intolerance clearly differs between ethnic groups, and *2*) the relationship between ethnicity and an abnormal glucose category is independent of the presence of other measured CV risk factors.

A few other studies have examined the relationship between diabetes, glu-

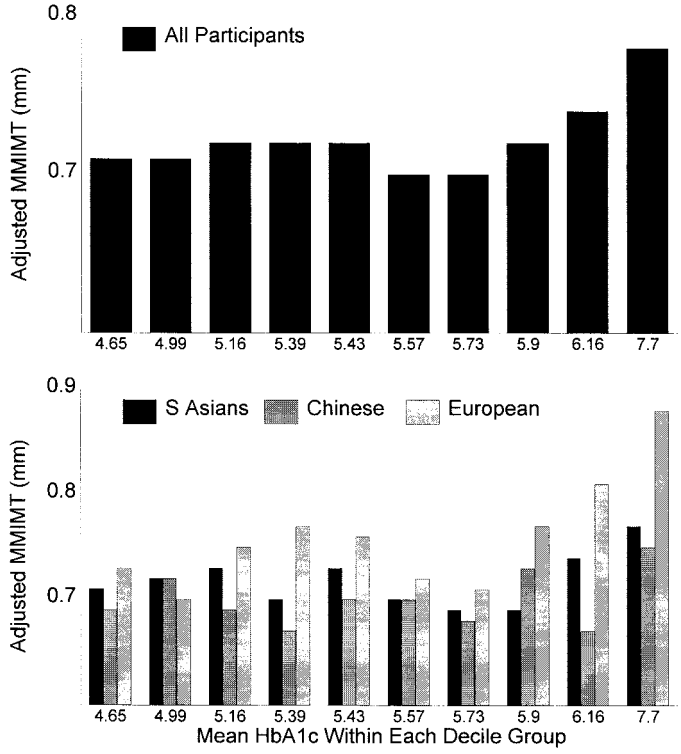

Figure 1—*The mean age- and sex-adjusted MMIMT within each group identified by decile is plotted against the mean HbA_{1c} within each decile group for all participants* (A) *and participants within each ethnicity* (B).

Table 5—*HbA_{1c} as an independent determinant of carotid atherosclerosis*

Relationship between MMIMT and HbA_{1c} after adjustment for:	β	*P*	MMIMT (mm) rise/0.9%* (95% CI)
Age and sex	0.03	<0.0001	0.0260 (0.0159–0.0362)
Age, sex, and ethnicity	0.03	<0.0001	0.0299 (0.0197–0.040)
Age, sex, ethnicity, and any diabetes	0.04	0.0001	0.0320 (0.0190–0.045)
Age, sex, and Ln-FFA	0.03	<0.0001	0.0263 (0.0159–0.0366)
Age, sex, Ln-FFA, and Ln-fTG HDL	0.03	<0.0001	0.0258 (0.0152–0.0363)
Age, sex, Ln-FFA, and Ln-fTG HDL ln-finsulin	0.03	<0.0001	0.0273 (0.0166–0.0380)
Age, sex, Ln-FFA, Ln-fTG HDL ln–Fasting insulin SBP, DBP, and WHR	0.03	<0.0001	0.0282 (0.0176–0.0387)
Age, sex, and Ln-HOMA-β	0.03	<0.0001	0.0230 (0.0124–0.0335)
Age, sex, and Ln-HOMA-IR	0.03	<0.0001	0.0278 (0.0166–0.0391)
Age, sex, Ln-HOMA-β, and Ln-HOMA-IR	0.02	0.0038	0.0202 (0.007–0.0339)

*0.9% = 1 SD of HbA_{1c}. FFA, fasting free fatty acid; fTG, fasting triglyceride; Ln, natural logarithm, WHR, waist-to-hip ratio.

cose, insulin resistance, and the anatomic extent of AS. Although people with diabetes were shown to have a higher IMT than nondiabetic people (14), significant associations between glucose levels, insulin levels, and carotid AS (15), or between insulin resistance and carotid AS (16–19), have not been consistently observed. Unfortunately, HbA_{1c} was not measured in these previous studies. Indeed, in at least two studies in which HbA_{1c} was measured, it was noted to be an important risk factor for carotid AS (20,21). These latter studies, as well as recent evidence that a period of glucose lowering with intensified insulin therapy reduced progression of carotid AS in people with type 1 diabetes who were in the Diabetes Control and Complications Trial (22), provide further support for the importance of HbA_{1c} as a powerful (and potentially modifiable) risk factor for AS.

The HbA_{1c} level reflects the fasting and postprandial glucose levels during a 2–3 month window (23). The fact that it was a strong determinant of AS suggests that it is to be preferred over other markers of dysglycemia (such as postload glucose) and may be the glycemic measure of choice when assessing risk for AS in both clinical practice and epidemiological research. The absence of a significant relationship between 2-h postload glucose and MMIMT, despite a strong relationship between AS and both HbA_{1c} and fasting glucose, may have been due to at least three possibilities. First, people with known diabetes did not have glucose tolerance testing in this study. Therefore, postload glucose measures were not available for these individuals, who presumably had the highest levels and the highest MMIMT. Second, few people with normal glucose tolerance have elevated fasting plasma glucose levels; for example, in one study of randomly selected patients in the U.S. (10), only 7.9% of 2,142 people with normal glucose tolerance had a fasting glucose level ≥6.1 mmol/l, whereas 33% of 2,932 people with normal fasting glucose levels already had a postload glucose level ≥7.8 mmol/l (10). Therefore, in nondiabetic individuals, elevated fasting plasma glucose is likely to reflect more advanced and perhaps longer-duration dysglycemia than an elevated postload glucose level, and it may therefore be more closely linked to MMIMT. Third, the high intrasubject variability of postload glucose levels may have obscured any relationship with MMIMT.

These data reflect a strong relationship between dysglycemia and AS that is independent of the presence or absence of diabetes. Moreover, the 0.032-mm difference in MMIMT that was noted per 0.9% rise in HbA_{1c} (after age, sex, ethnicity, and diabetes adjustment) (Table 5) is similar to the 0.036-mm difference in MMIMT observed between individuals taking 10 mg of ramipril and placebo during 4.5 years of follow-up in a substudy of the Heart Outcomes Prevention Evaluation Study (24,25). The fact that this study showed that ramipril reduced the risk of CV events by 22% suggests that modest differences in HbA_{1c} may reflect clinically relevant differences in CV risk.

Finally, these data do not explain why rising glucose levels are related to AS; nevertheless, they clearly support the inclusion of HbA_{1c} level in the list of AS risk factors in all people (not just those with diabetes). They also provide support for the hypothesis that therapies that lower glucose levels in people with even mod-

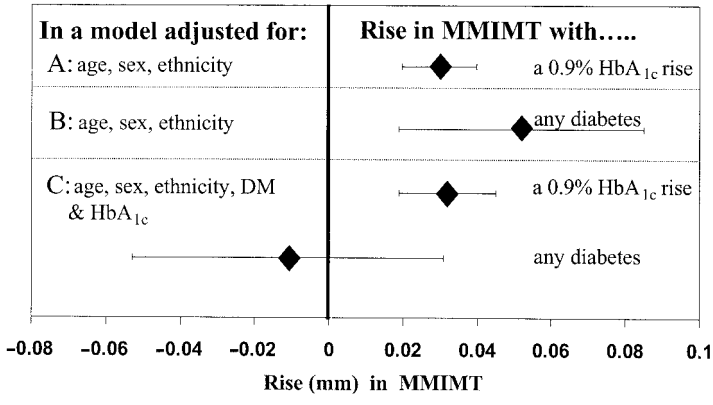

Figure 2— *Three regression models describing the relationship between the rise in carotid mean maximal IMT and either diabetes status or the rise in HbA_{1c}. All three models are adjusted for age, sex, and ethnicity. Model A shows the additional effect of diabetes, model B shows the additional effect of a rise in HbA_{1c} of 0.9% (1 SD), and model C shows the importance of both HbA_{1c} and diabetes when they are analyzed together.*

estly elevated levels may reduce the risk of AS.

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