Association of Carotid Intima-Media Thickness and Arterial Stiffness With Diabetic Retinopathy

The Chennai Urban Rural Epidemiology Study (CURES-2)

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OBJECTIVE — The aim of this study was to assess the association of intima-media thickness (IMT) and arterial stiffness with diabetic retinopathy in an Asian-Indian population that has very high prevalence rates of diabetes and coronary artery disease.

RESEARCH DESIGN AND METHODS — The study was conducted on 600 type 2 diabetic subjects randomly selected from the Chennai Urban Rural Epidemiology Study (CURES), which is an ongoing population-based study of a representative population of Chennai. When present, retinopathy was graded according to a modified Early Treatment Diabetic Retinopathy Study grading system. IMT was determined using high-resolution B-mode ultrasonography. Arterial stiffness was measured by assessing the augmentation index (AI) using the Sphygmocor apparatus.

RESULTS — Retinopathy was diagnosed in 116 of 590 (19.6%) subjects in whom retinal photography was possible. Mean values of IMT (0.93 ± 0.36 vs. 0.85 ± 0.21 mm, $P = 0.001$) and AI (27.9 ± 8.9 vs. 25.8 ± 9.6%, $P = 0.031$) were significantly higher among diabetic subjects with retinopathy compared with those without. Both IMT ($P = 0.024$) and AI ($P = 0.050$) showed a significant association to diabetic retinopathy, even after adjusting for age, duration of diabetes, HbA_{1c}, serum cholesterol, serum triglycerides, and microalbuminuria.

CONCLUSIONS — Diabetic retinopathy is associated with IMT and AI, suggesting that common pathogenic mechanisms might predispose to diabetic micro- and macroangiopathy.

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Diabetic vascular complications are classified into microangiopathy and microangiopathy, and it was earlier assumed that these were entirely different disease processes. However, the link between nephropathy, particularly microalbuminuria and cardiovascular disease, is becoming increasingly apparent (1). Recent studies (2,3) have shown that diabetic retinopathy is associated with atherosclerotic end points, but most of these studies have looked at the end stages of the atherosclerotic process. Since the clock for atherosclerosis starts ticking even before the onset of diabetes (4), it would be of interest to study whether structural changes, such as carotid intima-media thickness (IMT) (5), and functional changes, such as arterial stiffness (6), are associated with diabetic retinopathy. While a few studies (7–9) have looked at the association between IMT and diabetic retinopathy, to our knowledge there are no studies that have looked at the association of retinopathy with arterial stiffness. In this study we report on the association of IMT and arterial stiffness with retinopathy in a population-based study of Asian Indians, a high-risk group for diabetes (10) and coronary artery disease (CAD) (11).

RESEARCH DESIGN AND METHODS

The study subjects were recruited from the Chennai Urban Rural Epidemiology Study (CURES). CURES is an ongoing epidemiological study conducted on a representative population (aged ≥20 years) of Chennai (formerly Madras), the fourth largest city in India, with a population of ~4.2 million. The methodology of the study has been published elsewhere (12). Briefly, in phase 1 of the urban component of CURES, 26,001 individuals were recruited based on a systematic random sampling technique. Our website, www.mvdsc.org (under the link "Publications"), shows a map with the location of our center and the sampling frame. Self-reported diabetic subjects on drug treatment for diabetes were classified as "known diabetic subjects." Fasting capillary blood glucose was determined using a OneTouch Basic glucometer (Lifescan; Johnson & Johnson, Milpitas, CA) in all subjects. As the rural component of CURES has just commenced, rural subjects were not included in the study.

In phase 2 of CURES, all of the known diabetic subjects ($n = 1,529$) were invited to the center for detailed studies on vascular complications. In addition, all subjects with fasting blood glucose levels in the diabetic range based on American Diabetes Association fasting criteria (13) underwent oral glucose tolerance tests using

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Abbreviations: AI, augmentation index; CAD, coronary artery disease; CHS, Cardiovascular Health Study; CURES, Chennai Urban Rural Epidemiology Study; IMT, intima-media thickness.

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

a 75-g oral glucose load (dissolved in 250 ml of water). Subjects who had fasting plasma glucose levels <6.1 mmol/l (110 mg/dl) and 2-h plasma glucose values <7.8 mmol/l (140 mg/dl) were categorized as normal glucose tolerant. Those who were confirmed by oral glucose tolerance tests to have 2-h plasma glucose values ≥11.1 mmol/l (200 mg/dl), based on World Health Organization consulting group criteria (14), were labeled as "newly detected diabetic subjects." Using computer-generated random numbers, we selected 450 known diabetic subjects and 150 "newly diagnosed diabetic subjects " for the present study.

The sample size was calculated based on the following statistical assumptions: the prevalence of retinopathy among diabetic subjects in this population in our earlier study was 19.0% (95% CI 12.5–26.0) (15). Based on this, the ratio of retinopathic to nonretinopathic subjects was computed to be 1:4. To detect a mean IMT difference of 0.1 mm between subjects with and without retinopathy, with a type 1 error of 0.05, a type 2 error of 0.15, the SD for IMT in the population being 0.31 mm (16), and the ratio of case to control being 1:4, the required sample size was calculated to be 108 (PS, Power and Sample Size Calculations, version 2.1.30). Because the prevalence of diabetic retinopathy in the population is 19.0%, in order to obtain 108 subjects with diabetic retinopathy, we recruited 600 type 2 diabetic subjects for the study. Our earlier study has shown that retinopathy is present in 7.3% of newly detected diabetic subjects (17). The ratio of known to newly detected type 2 diabetes cases in India varies from 2:1 to 3:1 (18,19). Hence, known and newly detected diabetic subjects were recruited at a ratio of 3:1.

Anthropometric measurements including weight, height, and waist measurements were obtained using standardized techniques. BMI was calculated using the following formula: weight (in kilograms)/height (in meters squared). Blood pressure was recorded in the right arm, with the subject in the sitting position, to the nearest 2 mmHg with a mercury sphygmomanometer (Diamond Deluxe BP Apparatus; Industrial Electronic and Allied Products, Electronic Co-op Estate, Pune, India). Two readings were taken 5 min apart, and the mean of the two was taken as the blood pressure. The monthly income of the family was computed as the combined income of husband and wife taken as a single unit. Family income was graded as 1 (≤5,000 rupees), 2 (5,001–10,000), and 3 (>10,000) (1 USD = ~45 Indian rupees).

A fasting blood sample was taken for the estimation of plasma glucose and serum lipids. Biochemical assays were carried out using a Hitachi 912 Autoanalyzer (Roche Diagnostics, Mannheim, Germany) using kits supplied by Boehringer Mannheim (Mannheim, Germany). HbA_{1c} was estimated by the high-pressure liquid chromatography method using the Variant machine (BioRad, Hercules, CA).

Urine samples were collected in the early morning after an overnight fast. Urine creatinine was measured using Jaffe's method. Urinary protein was measured on spot urine by the sulfosalicylic acid technique (20). Expected protein excretion was calculated, and overt proteinuria was defined as ≥500 mg/day (20). Urine microalbumin concentration was measured using commercially available immunoturbidimetric assay kits from Roche Diagnostics on a Hitachi 902 Autoanalyzer (Roche Diagnostics), as reported elsewhere (20). Microalbuminuria was diagnosed if the albumin-to-creatinine ratio exceeded 30 mg/g of creatinine (20). Subjects in whom the microalbumin level was above the upper limit of detection (>450 mg/l) were assigned a value of 450 mg/l.

For retinal examination, the pupils were dilated by instilling one drop each of phenylephrine 10% and tropicamide 1% in both eyes, and the drops were repeated until the best possible mydriasis was obtained. Four-field color retinal photography was carried out by a trained photographer with a Zeiss FF 450 plus camera using 35-mm color transparencies. The four fields taken were stereoscopic pictures of the macula, disc, superior temporal, and inferior temporal quadrants, and this has been validated by us earlier (17). If photography of a particular eye or any field was not possible due to inadequate dilatation, inability to cooperate, or opacities of the media, these were specified as missing eye or fields.

Grading of retinal photographs were done using an identification number and assessed in a masked manner to minimize any possible bias. The photographs were graded for severity of retinopathy against standard photographs from the Early Treatment Diabetic Retinopathy Study grading system (21).

The minimum criterion for diagnosis of diabetic retinopathy was the presence of at least one definite microaneurysm in any field of the eye. Photographs were assessed and assigned a retinopathy level, and the final diagnosis for each patient was determined from the grading of the worse eye. Briefly, level 10 represents no retinopathy, levels 20–50 nonproliferative diabetic retinopathy, and level ≥60 proliferative diabetic retinopathy. Two independent graders graded the photographs. If there was disagreement between the graders, the photographs were graded by a third grader, and this was taken as the final diagnosis.

The early atherosclerotic markers studied were IMT and arterial stiffness. IMT of the carotid arteries was determined using a high-resolution B-mode ultrasonography system (Logic 400; GE, Milwaukee, WI) having an electric linear transducer midfrequency of 7.5 MHz. The images obtained were recorded and photographed. The scanning was done for an average of 20 min. The IMT was measured as the distance from the leading edge of the first echogenic line to the second echogenic line (5). Six well-defined arterial wall segments were measured in the right carotid system: the near wall and far wall of the proximal 10 mm of the internal carotid artery, the carotid bifurcation beginning at the tip of the flow divider and extending 10 mm below this point, and the arterial segment extending 10 mm below the bifurcation in the common carotid artery. Essential in defining these segments is the identification of a reliable longitudinal marker, which is the carotid flow divider as performed in SECURE (Study to Evaluate Carotid Ultrasound Changes in Patients Treated with Ramipril and Vitamin E) (22). This method was standardized at our center, and, to check quality, the video tapes were sent to Hamilton, Canada, the central laboratory for SECURE.

Arterial stiffness was measured using the Sphygmocor apparatus (Sphygmocor BPAS-1; PWV Medical, Sydney, Australia). A high-fidelity micromanometer (SPC-301; Millar Instruments, Houston, TX) was used to flatten but not occlude the right radial artery, using gentle pressure (23). The system software allowed

online recording of the peripheral waveform, and the integral software was used to generate an averaged peripheral and corresponding central waveform that was used for the determination of the augmentation index (AI). The AI was defined as the difference between the first and second peaks of the central arterial waveform, expressed as a percentage of the pulse pressure (6).

The AI is a measure of the contribution that the wave reflection makes to the arterial pressure waveform. The amplitude and timing of the reflected wave ultimately depends on the stiffness of the small vessels and large arteries; thus, the AI provides a measure of systemic arterial stiffness (6). We have previously shown good correlation among the AI, endothelial dysfunction measured by flow-mediated dilatation, and IMT (23).

Diabetes was diagnosed if the subjects were diagnosed by a physician based on blood tests or drug treatment for diabetes (insulin or oral hypoglycemic agents, for known diabetic subjects) or by a 2-h plasma glucose value ≥11.1 mmol/l (for newly detected diabetic subjects) (14).

Hypertension was diagnosed in all subjects who were on antihypertensive medication or had systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg.

CAD was diagnosed based on a past history of documented myocardial infarction and/or electrocardiographic changes suggestive of ST segment depression and/or Q-wave changes and/or T-wave changes using appropriate Minnesota codes (24). Drug treatment for CAD (aspirin or nitrates) was also diagnosed as CAD.

Individuals were classified as nonsmokers and current smokers (habitual smokers regardless of quantity smoked).

Quality controls

The interobserver agreement for assessment of retinal photographs was determined in a subset of 50 patients. Unweighted κ for agreement was 0.96, indicating good agreement. The reproducibility of the IMT measurement was examined by conducting another scan 1 week later on 20 subjects by the same sonographer. The mean difference in IMT between the first and second measurements was 0.02, the SD was 0.06, and the mean difference ranged between −0.09 and 0.09. To check for the reproducibility of the AI, two measurements were performed on 20 subjects on consecutive days by the same observer. The mean difference in AI between the first and second measurements was 1.35, the SD was 2.57, and the mean difference ranged between −4 and 5.

Statistical analysis

Statistical analysis was carried out with the SPSS package (version 4.0.1; Chicago, IL). Values are expressed as the means ± SD. Student's *t* test or one-way ANOVA, as appropriate, was used to compare continuous variables, and the χ^2 test was used to compare proportions among groups. To determine the confounding effect of various risk factors on the association of IMT and AI with retinopathy, regression analysis was done using diabetic retinopathy as the dependent variable and either IMT or AI as an independent variable. Different models were constructed using multivariate regression analysis to determine the association of IMT and AI with retinopathy by adjusting for other risk variables. The risk variables used were the ones that had a significant association with diabetic retinopathy on univariate regression (i.e., age, fasting plasma glucose, HbA_{1c}, duration of diabetes, microalbuminuria, proteinuria, creatinine, serum cholesterol, serum triglycerides, and CAD) and also have been shown to have an association both with diabetic retinopathy and CAD. Waist circumference and BMI were excluded because there is no biologically plausible mechanism to associate these variables with diabetic retinopathy. In the multivariate analysis, in order to avoid colinearity, CAD (because cholesterol and triglyceride levels are strong contributory factors), fasting plasma glucose (which is strongly associated with HbA_{1c}), creatinine, and proteinuria (because microalbuminuria is early indicator for renal disease) were not included.

RESULTS — None of the 600 study subjects provided a history of ketoacidosis or had evidence of ketonuria; therefore, all presumably had type 2 diabetes.

Of the subjects recruited, in one subject photographs could not be taken in both eyes because of dense cataracts. In two subjects, the photographs could not be taken in one eye because of bullous keratopathy and pthysical eye, respectively. Of the remaining 597 subjects, in 590 subjects (98.5%) photographs of both eyes could be graded. In 473 (80.2%), the quality of photographs was excellent, and in 117 (19.8%), the quality was good to satisfactory. In 25 (4.2%) patients, the photographs of some fields in one eye could not be graded due to various reasons (e.g., cataract).

The overall prevalence of diabetic retinopathy in the study population was 116 of 590 (19.6%). One-hundred ten subjects had nonproliferative diabetic retinopathy, and 6 had proliferative diabetic retinopathy. There was no difference in the prevalence of diabetic retinopathy between income grades (grade 1, 23.4%; grade 2, 15.3%; and grade 3, 20.3%; $P = 0.218$). Thirty-six subjects were related to each other (first degree) and were coded as relatives. The prevalence of retinopathy was not significantly different among relatives (16.7%) compared with nonrelatives (19.9%). There were no sibpairs among the retinopathic subjects.

Table 1 summarizes the baseline characteristics of the diabetic subjects with and without diabetic retinopathy. Mean values of IMT ($P = 0.001$) and AI ($P = 0.031$) were significantly higher among diabetic subjects with diabetic retinopathy compared with subjects without diabetic retinopathy (Table 1).

The effect of various risk factors on the association of IMT and AI with retinopathy was assessed using regression analysis (Table 2). IMT showed a strong association with retinopathy even after adjusting for age ($P = 0.032$), duration of diabetes ($P = 0.028$), fasting plasma glucose ($P = 0.006$), HbA_{1c} ($P = 0.006$), serum cholesterol ($P = 0.009$), serum triglycerides ($P = 0.003$), microalbuminuria ($P = 0.008$), proteinuria ($P = 0.007$), creatinine ($P = 0.015$), and CAD ($P = 0.009$). Similarly, the AI showed a strong association with retinopathy even after adjusting individually for all of the above parameters (fasting plasma glucose, $P = 0.021$; HbA_{1c}, $P = 0.037$; serum cholesterol, $P = 0.024$; serum triglycerides, $P = 0.018$; microalbuminuria, $P = 0.019$; proteinuria, $P = 0.027$; and creatinine, $P = 0.039$) except age, duration of diabetes, and CAD

Table 3 presents the results of the logistic regression analysis using diabetic retinopathy as the dependent variable. IMT ($P = 0.024$) and AI ($P = 0.050$) showed a significant association with diabetic retinopathy, even after adjust-

Table 1—*Clinical features of the study groups with and without retinopathy*

Variables	Without retinopathy	With retinopathy	*P*
n	474	116	—
Age (years)	52 ± 11	54 ± 11	0.016
Men	199 (42)	58 (50)	0.321
Duration of diabetes (years)	3 ± 4	7 ± 6	<0.001
BMI (kg/m^2)	25.5 ± 4.3	23.1 ± 3.7	<0.001
Waist circumference (cm)	91 ± 10	87 ± 10	<0.001
Systolic blood pressure (mmHg)	128 ± 18	131 ± 22	0.139
Diastolic blood pressure (mmHg)	78 ± 10	76 ± 11	0.082
Fasting plasma glucose (mmol/l)	8.6 ± 3.7	11.0 ± 4.5	<0.001
HbA_{1c} (%)	8.5 ± 2.0	10.0 ± 2.2	<0.001
Serum cholesterol (mmol/l)	5.22 ± 1.04	5.56 ± 1.41	0.004
HDL cholesterol (mmol/l)	1.14 ± 0.27	1.18 ± 0.26	0.205
LDL cholesterol (mmol/l)	3.21 ± 0.97	3.35 ± 1.18	0.187
Serum triglycerides (mmol/l)	1.90 ± 1.41	2.26 ± 1.67	0.019
Serum creatinine (μmol/l)	79.1 ± 15.4	83.1 ± 17.6	0.014
Proteinuria	24 (5.1)	20 (17.2)	<0.001
Microalbuminuria	120 (25.3)	60 (51.7)	<0.001
Smokers	43 (9.1)	8 (6.9)	0.455
Hypertension	150 (31.6)	42 (36.2)	0.347
CAD	60 (12.7)	25 (21.6)	0.014
Treatment for diabetes			
Newly detected diabetic subjects	141 (29.7)	7 (6.0)	—
Known diabetic subjects			
Diet	25 (5.3)	1 (0.9)	—
Oral drugs	282 (59.5)	76 (65.5)	<0.001
Insulin	7 (1.5)	10 (8.6)	—
Oral drugs + insulin	19 (4.0)	22 (19.0)	—
IMT (mm)			
Overall	0.85 ± 0.21	0.93 ± 0.36	0.001
Mild to moderate NPDR	—	0.93 ± 0.44*	—
Severe NPDR	—	0.95 ± 0.20†	—
PDR	—	0.86 ± 0.20	—
AI (%)			
Overall	25.8 ± 9.6	27.9 ± 8.9	0.031
Mild to moderate NPDR	—	27.6 ± 9.4	—
Severe NPDR	—	28.4 ± 8.3	—
PDR	—	27.8 ± 8.9	—

Data are means ± SD or *n* (%). *P = 0.001, compared with subjects with no diabetic retinopathy; †P = 0.038, compared with subjects with no diabetic retinopathy. NPDR, nonproliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy.

ing for age, duration of diabetes, HbA_{1c}, microalbuminuria, cholesterol, and triglycerides.

CONCLUSIONS — India currently has the largest number of diabetic patients in the world (10), and these numbers are still rising. This rapid increase is attributed to the epidemiological transition occurring in India (25). Transition in care factors such as screening and awareness also accompanies the epidemiological transition due to affluence and improved education, resulting in an increased number of detected cases. However, escalation in the prevalence of type 2 diabetes and improved survival result in increased atherosclerotic and microvascular complications.

Type 2 diabetes exposes the vasculature to the onslaught of several factors, namely hyperglycemia, hypertension, dyslipidemia, hemostatic changes, and inflammation (26). The association of the above factors with macrovascular disease (26) and with diabetic retinopathy (27,28) is well known. However, the association of diabetic retinopathy with early atherosclerotic markers has not been adequately explored, particularly in a non-European population. CURES gave us an opportunity to look at the association of diabetic retinopathy with early atherosclerotic markers in an epidemiological setting in Asian Indians, a population with a high prevalence of diabetes (10) and premature CAD (11).

Our finding that IMT showed a strong association with diabetic retinopathy is consistent with the findings of the Atherosclerosis Risk in Communities (ARIC) study (8) and a case-control study (9). However, the Cardiovascular Health Study (CHS) (7) did not show a relationship between early atherosclerosis and diabetic retinopathy. The discrepancy is likely explained by the differences in the ages of the populations studied (ARIC study: 51–72 years of age, CHS: 69–102 years of age). However, in the CHS study, those with clinically evident CAD showed a strong association with diabetic retinopathy. Furthermore, in the latter study, although the prevalence of diabetic retinopathy increased with an increase in IMT up to 1.78 mm, this did not reach statistical significance, probably due to the small number of subjects with diabetic retinopathy (n = 80). An earlier study (29) on young type 1 diabetic patients reported that carotid atherosclerosis was associated with diabetic retinopathy. The present study of type 2 diabetic subjects showed that carotid IMT had a strong association with diabetic retinopathy even after adjusting for age, duration of diabetes, and HbA_{1c}.

Arterial stiffness, measured as AI using pulse-wave analysis, has been shown (30) to have good correlation with cardiovascular end points. Our study showed that the mean AI was higher in subjects with diabetic retinopathy compared with the group without retinopathy. This is the first study to demonstrate an association of diabetic retinopathy with functional change in arteries as measured by arterial stiffness.

The association between microalbuminuria and cardiovascular mortality is well known (1), and an association of microalbuminuria with IMT has also been demonstrated (31). Hence one could argue that the relation between diabetic retinopathy and atherosclerosis noted in this study could probably be due to the associated nephropathy. However, the association of both IMT and arterial stiffness

Table 2—*Association of IMT and AI with diabetic retinopathy after individually adjusting for different risk variables*

	Diabetic retinopathy and IMT		Diabetic retinopathy and AI	
Variable	Odds ratio (95% CI)	*P*	Odds ratio (95% CI)	*P*
Age	2.659 (1.087–6.50)	0.032	1.019 (0.996–1.042)	0.105
Sex	3.390 (1.435–8.006)	0.005	1.030 (1.007–1.054)	0.010
BMI	2.851 (1.209–6.725)	0.017	1.016 (0.994–1.039)	0.160
Waist circumference	3.308 (1.412–7.746)	0.006	1.018 (0.998–1.041)	0.116
Duration of diabetes	2.383 (1.099–5.169)	0.028	1.019 (0.995–1.044)	0.121
Fasting plasma glucose	3.461 (1.421–8.432)	0.006	1.028 (1.004–1.052)	0.021
HbA_{1c}	3.463 (1.419–8.449)	0.006	1.025 (1.001–1.049)	0.037
Serum cholesterol	3.159 (1.336–7.470)	0.009	1.026 (1.003–1.049)	0.024
Serum triglycerides	3.642 (1.536–8.636)	0.003	1.027 (1.005–1.050)	0.018
Microalbuminuria	3.17 (1.35–7.4)	0.008	1.03 (1.004–1.057)	0.019
Proteinuria	3.207 (1.368–7.520)	0.007	1.026 (1.003–1.043)	0.027
Creatinine	2.928 (1.228–6.980)	0.015	1.024 (1.001–1.046)	0.039
CAD	3.031 (1.312–7.001)	0.009	1.021 (0.999–1.044)	0.066

Logistic regression analysis was done using diabetic retinopathy as the dependent variable and either IMT or AI as the independent variable. The odds ratios were determined after individually adjusting for the variables shown in the first column.

with diabetic retinopathy persisted even after adjusting for microalbuminuria (and proteinuria), suggesting that retinopathy per se is associated with early atherosclerosis. Several of the risk factors for macrovascular disease, such as hyperglycemia, hypertension, dyslipidemia, hemostatic changes, and inflammation, have also been shown (27,28) to be associated with retinopathy.

Because this is a cross-sectional study, the association between diabetic retinopathy and early atherosclerosis cannot be taken as a cause-and-effect relationship. Furthermore, as the study is based on 600 randomly selected diabetic subjects, extrapolating these results to the general population should be done with caution. However, the selection process has ensured that the study subjects are representative of the population. Moreover, the prevalence of diabetic retinopathy obtained in this study is similar to that observed in our earlier population-based study (15). Finally, the techniques used for determining diabetic retinopathy (15,17), IMT (16,22,23), and AI (6,16,23) are robust and have been validated previously.

In summary, our data show that there is an association between early atherosclerosis and diabetic retinopathy in this urban south Indian population, suggesting that common pathogenic factors might contribute to the development of both micro- and macroangiopathy.

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Preliminary data from this study were pre-

Table 3—*Logistic regression analysis using diabetic retinopathy as the dependent variable*

	Model 1		Model 2		Model 3	
Variables	Odds ratio (95% CI)	*P*	Odds ratio (95% CI)	*P*	Odds ratio (95% CI)	*P*
Diabetic retinopathy and IMT						
IMT	3.6 (1.51–8.46)	0.004	2.9 (1.17–7.33)	0.022	2.9 (1.15–7.29)	0.024
Age	—	—	0.99 (0.96–1.01)	0.231	0.99 (0.96–1.01)	0.268
Duration of diabetes	—	—	1.14 (1.09–1.19)	<0.001	1.14 (1.09–1.19)	<0.001
HbA_{1c}	—	—	1.25 (1.12–1.39)	<0.001	1.25 (1.12–1.39)	<0.001
Microalbuminuria	—	—	1.003 (1.001–1.005)	0.001	1.003 (1.001–1.004)	0.003
Serum cholesterol	—	—	—	—	1.000 (0.995–1.006)	0.928
Serum triglycerides	—	—	—	—	1.01 (0.999–1.003)	0.225
Diabetic retinopathy and AI						
AI	1.025 (1.002–1.047)	0.035	1.026 (1.0001–1.0533)	0.050	1.026 (1.0001–1.0529)	0.050
Age	—	—	0.99 (0.97–1.01)	0.415	0.99 (0.97–1.02)	0.463
Duration of diabetes	—	—	1.13 (1.09–1.19)	<0.001	1.13 (1.08–1.19)	<0.001
HbA_{1c}	—	—	1.25 (1.12–1.39)	<0.001	1.24 (1.12–1.39)	<0.001
Microalbuminuria	—	—	1.003 (1.001–1.005)	0.001	1.003 (1.001–1.005)	0.002
Serum cholesterol	—	—	—	—	1.001 (0.995–1.007)	0.740
Serum triglycerides	—	—	—	—	1.001 (0.999–1.003)	0.240

sented at the 63rd American Diabetes Association meeting at New Orleans in June 2003.

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