Increased Intimal-Medial Thickness in Newly Detected Type 2 Diabetes

Risk factors

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OBJECTIVE — To examine carotid intimal-medial thickness (IMT) and its determinants in newly detected type 2 diabetic subjects, classified according to the new criteria of the American Diabetes Association, in comparison with age- and sex-matched control subjects with normal glucose tolerance.

RESEARCH DESIGN AND METHODS — This study was case-controlled, with matched pairs for 71 newly diagnosed type 2 diabetic individuals. Subjects aged 40–70 years were recruited from a risk population for diabetes seen in the Risk Factors in IGT for Atherosclerosis and Diabetes (RIAD) Study. Standard risk factors, 75-g oral glucose tolerance test with real insulin, proinsulin, and C-peptide, and ultrasound measurement of the IMT of the common carotid artery were performed.

RESULTS — The diabetic subjects, both men and women, displayed carotid intimal-medial thickening, even in the subgroup with fasting plasma glucose between 7.0 and 7.8 mmol/l. HbA_{1c} was significantly increased in the diabetic patients (6.33 vs. 5.48%). Insulin, proinsulin, and C-peptide were also significantly higher. Among the coronary risk factors, triglycerides and plasminogen activator inhibitor were significantly increased. After age and sex adjustment, IMT in the diabetic group was correlated to triglycerides and the total-to-HDL cholesterol ratio. In the total group, IMT was significantly correlated to blood pressure, 2-h glucose in oral glucose tolerance testing, triglycerides, albuminuria, and the total-to-HDL cholesterol ratio, and inversely correlated to HDL cholesterol. No independent determinant of IMT was found in the diabetic group by multivariate analysis.

CONCLUSIONS — Newly detected type 2 diabetic patients exhibit a higher degree of early atherosclerosis than normal glucose-tolerant subjects matched for age and sex. Our data suggest that hyperglycemia, together with a clustering of risk factors, and in particular dyslipidemia, may cause intimal-medial thickening in the early phases of diabetes.

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Type 2 diabetes is known to be associated with an excessively high rate of mortality and morbidity from macrovascular diseases (1–6). Atherosclerosis, unless in a severe form, is often asymptomatic, however, so that a direct examination of the vessel wall is necessary to detect affected individuals in the early stages. Measurement of the intimal-medial thickness (IMT) of the common carotid artery (CCA) by B-mode ultrasound was found to be a suitable noninvasive method to visualize the arterial walls and to monitor the early stages of the atherosclerotic process (7–12). The thickness of the CCA was demonstrated to be related to cardiovascular risk factors and to the occurrence of coronary heart disease (CHD) (13–15).

An increased carotid IMT was observed in type 2 diabetic patients (16–21). Furthermore, asymptomatic hyperglycemic subjects were shown to have significant intimal-medial thickening in comparison with healthy control subjects (22). The new American Diabetes Association criteria for the diagnosis of diabetes (23) are derived from evidence that microvascular alterations precede the old cutoff limits for diabetes (24). Furthermore, the hypothesis has been raised that the clock for macrovascular disease could also start ticking before the onset of clinical diabetes (25). So far, there is no information on early atherosclerosis measured by ultrasound in newly diagnosed type 2 diabetes classified according to the new American Diabetes Association criteria.

We therefore examined IMT of the CCA in newly detected type 2 diabetic patients, defined in accordance with the new recommendations, in comparison with age- and sex-matched control subjects with normal glucose tolerance. In addition, we investigated the relationship between various risk factors and IMT in these subjects.

RESEARCH DESIGN AND METHODS

— Diabetic patients and control subjects from the Risk Factors in IGT for Atherosclerosis and Diabetes (RIAD) Study, a prospective survey on risk factors for atherosclerosis and diabetes in patients with impaired glucose tolerance, were analyzed. Details of study design and participants have been published (26,27). Briefly, middle-aged subjects (40–70 years) with risk factors for the development of diabetes, such as familial history of type 2 diabetes, obesity, and/or dyslipoproteinemia were examined if they had no known diabetes and were on no medication that could affect glucose tolerance (thiazide diuretics, β-blockers, corticosteroids). The

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Abbreviations: CCA, common carotid artery; CHD, coronary heart disease; CV, coefficient of variation; FPG, fasting plasma glucose; IMT, intimal-medial thickness; OGTT, oral glucose tolerance test; PAI-1, plasminogen activator inhibitor; RIAD, Risk Factors in IGT for Atherosclerosis and Diabetes; tPA, tissue plasminogen activator.

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

RIAD participants underwent examination, including the following: measurement of blood pressure, waist-to-hip ratio, and BMI; standard oral glucose tolerance test (OGTT) with 75 g glucose; questionnaire for lifestyle, medical history, and medication; examination of accepted risk factors for atherosclerosis; and ultrasound examination of the carotid and femoral arteries.

In this work, we analyzed data from the newly detected type 2 diabetic subjects (n = 71; 23 women and 48 men), diagnosed based on a fasting plasma glucose (FPG) >7.0 mmol/l and/or a 2-h plasma glucose in OGTT >11.1 mmol/l. Control subjects were selected from the RIAD participants with FPG <7.0 mmol/l and 2-h plasma glucose <7.8 mmol/l. The case-control pairs were matched one-to-one by sex and age. The quality of matching was checked by conducting bivariate correlation for age in the groups (r = 0.995, $P < 0.001$).

In the diabetic group, 10 subjects had a positive history for CHD and none for stroke or peripheral arterial occlusion. Similarly, 10 of the control subjects had a history of CHD and, in addition, one subject for stroke and one for peripheral arterial occlusion. There were four smokers among the diabetic patients and nine smokers in the control group. From the test group, 9.9% of the subjects were treated with ACE inhibitors (vs. 7.0% of the control subjects) and 9.9% were on calcium-channel blockers (vs. 5.6% of the control subjects). The clinical and biochemical characteristics of the examined subjects are shown in Table 1.

Anthropometric determinations

Weight and height were measured by standard techniques. BMI was calculated as the body weight (in kilograms) divided by height squared (in meters squared). The waist circumference was determined with a plastic tape at the midpoint between the lower rib margin and the iliac crest, and the hip circumference, at the level of the trochanter. The ratio between them provided the waist-to-hip ratio.

Ultrasound measurement

B-mode ultrasound of the CCA was performed with the Acuson 128XP Computed Sonography System (Acuson, Mountain View, CA) using a 10-MHz linear array transducer, as previously published (26,27). Briefly, we measured the IMT of the far wall of the CCA, as originally described by Pignoli et al. (7). To avoid variability during the cardiac cycle, the images were frozen in the end-diastolic phase. IMT was measured twice bilaterally in the distal CCA, and the mean of these values represented the IMT_{mean} of each subject. In addition, the maximal thickness of the CCA was measured independently of the localization (IMT_{max}). The examination was performed on the day of blood collection for laboratory analysis, so that both patients and physicians were unaware of the corresponding laboratory values. The reproducibility of the IMT measurement was checked by a second scan within 3 months from baseline in 24 subjects. The mean difference in IMT between these two examinations was 0.01 mm, and the correlation between them was 0.916 for the right CCA IMT, 0.957 for the left CCA IMT, 0.969 for IMT_{max}, and 0.984 for IMT_{mean}, indicating good reproducibility.

Laboratory examination

Standard OGTT was conducted with 75 g glucose (Glucodex; Rougier, Chambly, Que-

Table 1—*Clinical and biochemical characteristics of diabetic patients and control subjects*

	Control subjects	Diabetic patients	*P*
n	71	71	—
Sex (F/M)	23/48	23/48	—
Age (years)	57.0 ± 0.8 (55.3–58.6)	57.0 ± 0.8 (55.3–58.6)	NS
Smoking (%)	12.7	5.6	NS
BMI (kg/m^2)	27.4 ± 0.4 (26.6–28.2)	28.8 ± 0.4 (28.0–29.7)	0.02
Waist-to-hip ratio	0.92 ± 0.009 (0.90–0.94)	0.95 ± 0.01 (0.93–0.97)	NS
Systolic blood pressure (mmHg)	137.0 ± 2.3 (132.4–141.6)	141.4 ± 2.2 (137.1–145.7)	NS
Diastolic blood pressure (mmHg)	85.7 ± 1.2 (83.4–88.0)	85.8 ± 1.1 (83.6–88.0)	NS
FPG (mmol/l)	5.52 ± 0.04 (5.45–5.60)	7.50 ± 0.18 (7.15–7.85)	<0.001
2-h plasma glucose in OGTT (mmol/l)	5.92 ± 0.13 (5.76–6.09)	11.90 ± 0.44 (11.5–13.3)	<0.001
HbA_{1c} (%)	5.48 ± 0.04 (5.39–5.57)	6.33 ± 0.11 (6.11–6.56)	<0.001
Real insulin (pmol/l)	76.6 ± 5.9 (64.8–88.4)	115.4 ± 9.4 (96.7–134.2)	<0.001
Proinsulin (pmol/l)	1.74 ± 0.15 (1.45–2.04)	4.92 ± 0.58 (3.76–6.08)	<0.001
C-peptide (pmol/l)	1160.1 ± 52.9 (1054.5–1265.7)	1495.7 ± 70.6 (1354.7–1636.7)	<0.001
Total cholesterol (mmol/l)	5.75 ± 0.12 (5.52–5.98)	6.00 ± 0.14 (5.73–6.27)	NS
Triglycerides (mmol/l)	1.45 ± 0.11 (1.23–1.67)	3.10 ± 0.44 (2.22–3.99)	0.001
HDL cholesterol (mmol/l)	1.38 ± 0.06 (1.27–1.50)	1.26 ± 0.05 (1.16–1.35)	NS
Total-to-HDL cholesterol ratio	4.72 ± 0.30 (4.13–5.32)	5.30 ± 0.28 (4.74–5.86)	NS
$PAI\text{-}1_{active}$ (ng/ml)	42.7 ± 4.5 (33.7–51.7)	62.2 ± 5.5 (51.2–73.3)	0.007
von Willebrand factor (%)	116 ± 7.8 (101.1–132.2)	105 ± 5.3 (94.5–115.6)	NS
Fibrinogen (g/l)	2.93 ± 0.08 (2.78–3.09)	3.13 ± 0.08 (2.96–3.30)	NS
tPA (ng/ml)	10.04 ± 0.36 (9.31–10.77)	11.80 ± 0.59 (10.61–12.98)	0.01
Albuminuria (mg/l)	11.5 ± 1.41 (7.37–15.5)	19.7 ± 4.85 (5.13–34.1)	NS
IMT_{mean} (mm)	0.85 ± 0.02 (0.82–0.89)	0.98 ± 0.03 (0.93–1.03)	<0.001
IMT_{max} (mm)	0.99 ± 0.03 (0.93–1.05)	1.10 ± 0.03 (1.05–1.21)	0.015

Data are means ± SEM (95% CI).

bec, Canada). HbA_{1c} was examined by high performance liquid chromatography on a Diamat analyzer (Bio-Rad Laboratories, Munich, Germany). Plasma glucose was measured by the hexokinase method (interassay coefficient of variation [CV] = 1.5%). HDL cholesterol was examined by precipitation with dextran sulfate (Ciba Corning Diagnostics, Fernwald, Germany). Triglycerides and total cholesterol were measured by enzyme colorimetric assays on a Ciba Corning Express Plus analyzer, using commercially available test kits (Boehringer Mannheim, Mannheim, Germany). Proinsulin was measured by enzyme immunoassay (DGR Instruments, Marburg, Germany). The monoclonal antibody used in this assay recognizes a proinsulin specific epitope. Specific insulin and C-peptide were also measured by enzyme immunoassay (Medgenix Diagnostics, Fleurus, Belgium). Specific insulin (interassay CV = 7.6%) showed no cross-reactivity to human proinsulin. The concentration of active plasminogen activator inhibitor-1 (PAI-1) antigen was determined using commercially available enzyme immunoassays (Immuno AG, Heidelberg, Germany). Tissue plasminogen activator (tPA) was measured by enzyme immunoassay (TintElize; Biopool, Umea, Sweden), fibrinogen by the method of Clauss (Fibrinogen; Boehringer Mannheim), and von Willebrand factor antigen by electroimmunoassay (Immuno AG). Urine was collected as fresh urine samples. Albuminuria was measured by nephelometry (Nephelometer BNII; Behring, Marburg, Germany).

Statistics

Data evaluation was conducted using the SPSS/PC+ program. Metabolic parameters were compared by *t* test or Mann-Whitney *U* test, if necessary. The level of significance was determined by $P < 0.05$. Data are presented as means ± SEM and 95% CIs. The χ^2 test was used to check the difference between the two groups with respect to smoking, antihypertensive treatment, and history of macrovascular disease. The correlations between IMT and risk factors were assessed using Pearson or Spearman correlation coefficients, as appropriate. In addition, partial correlation after adjustment for age was evaluated. Multivariate analysis was performed by linear regression.

RESULTS — The diabetic and control groups were thoroughly matched for age and sex (Table 1). There was no significant difference for history of macrovascular disease, percentage of smokers, or antihypertensive treatment. The diabetic patients displayed significantly higher BMIs, whereas waist-to-hip ratio was similar (Table 1). No significant difference between the two groups was found for either systolic or diastolic blood pressure. Plasma glucose, both fasting and 2-h postprandial in OGTT, as well as HbA_{1c}, were significantly higher in the newly detected type 2 diabetic subjects. Similarly, all insulin fractions, real insulin, proinsulin, and C-peptide, were significantly increased in the diabetic group. Total cholesterol was slightly higher and HDL cholesterol somewhat lower in the diabetic group, although the difference did not reach statistical significance. Plasma triglycerides were significantly higher in the diabetic subjects. The fibrinolytic parameters, $PAI\text{-}1_{active}$ and tPA, were significantly increased in the diabetic group, whereas fibrinogen and von Willebrand factor did not differ. The diabetic individuals displayed a higher PAI-to-tPA ratio (5.32 ± 0.46 vs. 4.18 ± 0.42 in control subjects), which was not of statistical significance. Albuminuria in the diabetic subjects was increased without being statistically significant.

The newly detected diabetic patients displayed an increased IMT of the CCA, which was statistically significant for both IMT_{mean} and IMT_{max} (Table 1). These results were confirmed when women and men were analyzed separately. The carotid IMT in female diabetic subjects was higher in comparison to that of the female control subjects (0.94 ± 0.04 vs. 0.79 ± 0.02 mm; $P = 0.003$). Similarly, IMT in diabetic men was increased compared with that in the nondiabetic men (1.0 ± 0.03 vs. 0.88 ± 0.03 mm; $P = 0.008$). To assess the impact of the new diabetes criteria on IMT values, we divided the diabetic subjects according to the level of FPG into the following groups: *1*) FPG <7.0 mmol/l ($n = 19$), *2*) FPG between 7.0 and 7.8 mmol/l ($n = 34$), and *3*) FPG >7.8 mmol/l ($n = 18$). There was no significant difference between these groups with respect to carotid IMT (group 1 = 1.01 mm; group 2 = 0.96 mm; group 3 = 0.98 mm); however, all of them had significantly increased IMT in comparison to the control subjects.

The distribution of carotid IMT in the diabetic and control groups, with a shift to a thicker arterial wall in the diabetic individuals, is presented in Fig. 1.

In univariate analysis, age, systolic and diastolic blood pressures, and ratio of total-to-HDL cholesterol were found to be significantly positively and HDL cholesterol significantly inversely correlated to carotid IMT in the nondiabetic subjects (Table 2). In addition, waist-to-hip ratio, total cholesterol, triglycerides, fasting and 2-h plasma glucose in OGTT, and albuminuria were indicative for carotid IMT for

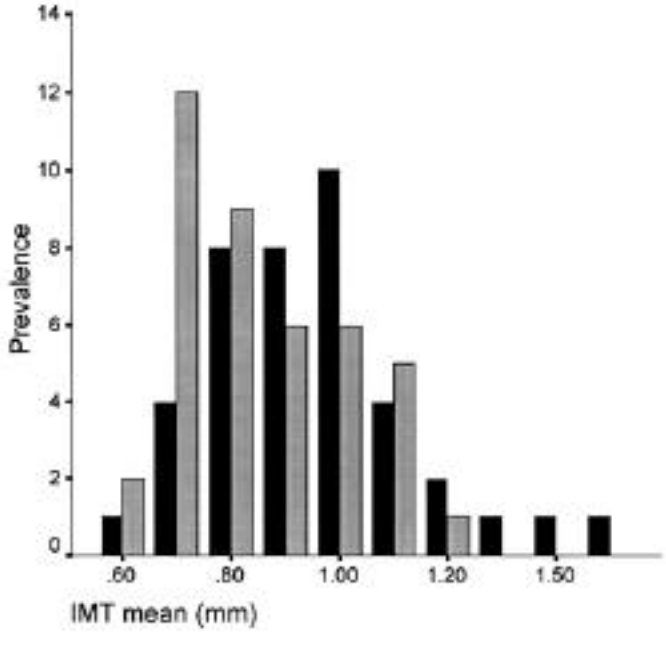

Figure 1—*Distribution of carotid IMT_{mean} (in millimeters) in type 2 diabetic patients (■) and nondiabetic control subjects (■) matched for age and sex.*

Table 2—*Correlation of IMT to risk factors in diabetic patients and control subjects and in the total group*

	Unadjusted			Age- and sex-adjusted		
	Control subjects (*P*)	Diabetic patients (*P*)	Total (*P*)	Control subjects (*P*)	Diabetic patients (*P*)	Total (*P*)
Age	0.26 (0.03)	0.15 (NS)	0.19 (0.03)	—	—	—
BMI	−0.12 (NS)	−0.05 (NS)	−0.01 (NS)	0.01 (NS)	0.02 (NS)	0.03 (NS)
Waist-to-hip ratio	0.22 (NS)	0.16 (NS)	0.22 (0.01)	0.06 (NS)	0.13 (NS)	0.09 (NS)
Systolic blood pressure	0.24 (0.05)	0.14 (NS)	0.21 (0.02)	0.27 (0.07)	0.02 (NS)	0.19 (0.04)
Diastolic blood pressure	0.28 (0.02)	0.18 (NS)	0.21 (0.01)	0.26 (0.07)	0.21 (NS)	0.19 (0.04)
FPG	0.02 (NS)	−0.03 (NS)	0.19 (0.02)	0.1 (NS)	−0.13 (NS)	0.15 (NS)
2-h plasma glucose in OGTT	−0.09 (NS)	0.13 (NS)	0.28 (0.001)	−0.15 (NS)	0.12 (NS)	0.22 (0.001)
HbA_{1c}	−0.04 (NS)	−0.05 (NS)	0.13 (NS)	−0.13 (NS)	−0.13 (NS)	0.09 (NS)
Total cholesterol	0.08 (NS)	0.17 (NS)	0.16 (0.05)	0.02 (NS)	0.22 (NS)	0.15 (NS)
Triglycerides*	0.14 (NS)	0.19 (NS)	0.24 (0.004)	0.3 (0.04)	0.33 (0.03)	0.25 (0.006)
HDL cholesterol	−0.3 (0.01)	−0.19 (NS)	−0.27 (0.001)	−0.31 (0.03)	−0.24 (NS)	−0.27 (0.002)
Total-to-HDL cholesterol ratio	0.37 (0.002)	0.24 (0.05)	0.31 (<0.001)	0.36 (0.01)	0.33 (0.03)	0.28 (0.009)
Real insulin*	−0.05 (NS)	−0.08 (NS)	0.02 (NS)	−0.03 (NS)	−0.16 (NS)	0.02 (NS)
Proinsulin	−0.03 (NS)	−0.13 (NS)	0.02 (NS)	0.04 (NS)	−0.24 (NS)	0.02 (NS)
C-peptide	−0.04 (NS)	−0.09 (NS)	0.02 (NS)	0.01 (NS)	−0.15 (NS)	0.02 (NS)
$PAI\text{-}1_{active}$	−0.03 (NS)	0.01 (NS)	0.08 (NS)	0.02 (NS)	0.14 (NS)	0.16 (NS)
von Willebrand factor	−0.12 (NS)	0.01 (NS)	−0.09 (NS)	−0.12 (NS)	0.07 (NS)	−0.09 (NS)
Fibrinogen	−0.06 (NS)	0.23 (NS)	0.15 (NS)	−0.07 (NS)	0.23 (NS)	0.16 (NS)
tPA	0.05 (NS)	0.14 (NS)	0.18 (NS)	−0.01 (NS)	0.19 (NS)	0.14 (NS)
Albuminuria*	0.18 (NS)	0.25 (NS)	0.27 (0.007)	0.4 (0.006)	0.19 (NS)	0.24 (0.03)

**P* determined using Spearman's correlation; for all other parameters: *P* was determined using Pearson's correlation.

the total group. If analyzing the diabetic subjects separately, IMT was correlated only to the total-to-HDL cholesterol ratio. In the nondiabetic subjects, after adjustment for age and sex albuminuria, triglycerides and the total-to-HDL cholesterol ratio were significantly positively correlated to IMT, and HDL cholesterol was inversely correlated to IMT. These correlations were also found to exist for the total group, with a significant correlation of IMT to blood pressure and 2-h plasma glucose in OGTT. In the diabetic individuals, triglycerides and the total-to-HDL cholesterol ratio were significantly correlated to IMT after adjustment for age and sex. In multivariate analysis, no independent determinant of IMT was found in the newly detected diabetic patients. Since results for IMT_{mean} and IMT_{max} were essentially the same, they were not presented separately.

The prevalence of different atherosclerosis risk factors, alone or in combination, in the examined type 2 diabetic subjects and their impact on carotid IMT is shown in Table 3.

CONCLUSIONS — The present study provides data for the increased carotid IMT in middle-aged newly detected type 2 diabetic subjects with a slightly elevated HbA_{1c} level (mean value 6.33%; reference values from our laboratory 4.8–5.9%). IMT was significantly increased, even in the diabetic subgroup with FPG between 7.0 and 7.8 mmol/l. Carotid IMT is a generally

Table 3—*Impact of atherosclerosis risk factors on IMT*

Combination	*n*	IMT_{mean} (mm)
Diabetes	2	0.88 ± 0.13
Diabetes + hypertension	3	0.88 ± 0.06
Diabetes + hypertension + smoking (mean)	2	0.8
Diabetes + hyperlipoproteinemia	7	0.94 ± 0.05
Diabetes + hyperlipoproteinemia + smoking (absolute value)	1	1.1
Diabetes + hyperlipoproteinemia + obesity	7	0.89 ± 0.6
Diabetes + hyperlipoproteinemia + obesity + smoking	2	0.88 ± 0.13
Diabetes + hyperlipoproteinemia + hypertension	13	1.01 ± 0.06
Diabetes + hyperlipoproteinemia + hypertension + smoking	6	1.03 ± 0.1
Diabetes + hyperlipoproteinemia + hypertension + obesity	23	1.01 ± 0.05
Diabetes + hyperlipoproteinemia + hypertension + obesity + smoking	2	1.08 ± 0.08

Data are means ± SEM unless otherwise indicated. Hypertension is defined as systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg or antihypertensive therapy. Smoking is defined as ≥1 cigarettes per day. Hyperlipoproteinemia is defined as total cholesterol ≥5.2 mmol/l, triglycerides ≥1.7 mmol/l, HDL cholesterol ≤1.1 (in women) or 1.0 mmol/l (in men), or lipid-lowering drugs. Obesity is defined as BMI ≥28 kg/m^2.

accepted good marker for early atherosclerosis (7–12), and particularly for coronary vascular disease (13–15). Recently, type 2 diabetes was convincingly shown to be associated with intimal-medial thickening (16–21). These studies, however, were performed in patients with already known diabetes who had a duration of ~10 years and HbA_{1c} in the range of 7.46 (19) to 9.65% (16) and were under various types of antidiabetic treatment. So far, there is no information available on the carotid IMT in newly diagnosed asymptomatic type 2 diabetic individuals in a middle-aged European population. Thus, the strength of this study is the careful recruitment of newly detected diabetic subjects, based on the new criteria for diabetes with the performance of a standard 75-g OGTT and thorough matching for age and sex with control subjects with normal glucose tolerance who have the same genetic and environmental background. Our findings confirm the notion that atherosclerosis starts before type 2 diabetes is diagnosed, as suggested by Haffner et al. (25).

The cause of early atherosclerosis in the beginning stages of type 2 diabetes could be sought in the glucose toxicity for endothelium and glycosylation processes, as indicated by the higher levels of plasma glucose and HbA_{1c} in the diabetic patients compared with control subjects, as well as in the significant increase in risk factors, such as dyslipidemia and impaired fibrinolysis. It is known that hyperglycemia may exert a direct toxic effect on cell function and structure through glycation products and other cellular abnormalities (28). Furthermore, hyperglycemia could act indirectly through an association with various interrelated metabolic disorders. Thus, dyslipidemia (29,30), hypertension (30,31), impaired fibrinolysis (30,32), microalbuminuria (31), and insulin resistance (33) were found to be indicative of carotid IMT.

Our finding that plasma triglycerides and total-to-HDL cholesterol ratio are significantly correlated with IMT in diabetic subjects is in agreement with other reports on the crucial role of dyslipidemia in the excessive cardiovascular mortality associated with type 2 diabetes that has been established in prospective studies (4,34,35). In the studies of Geroulakos et al. (17) and Kanters et al. (18), no conventional risk factor was associated with IMT in patients with already known diabetes. Kawamori et al. (16) found smoking, hyperlipoproteinemia, duration of diabetes, hypertension, and age to be indicative of IMT in type 2 diabetic patients with an average HbA_{1c} level of 8.4–9.6% and duration of diabetes of 8.8–17.7 years. Pujia et al. (19) reported that blood pressure was the only significant determinant of IMT in diabetic patients with HbA_{1c} of 7.46% and diabetes duration of 10.7 years. Among diabetic patients in the Insulin Resistance Atherosclerosis Study, established diabetes and fasting glucose level were each independently associated with CCA IMT (20). In elderly Finnish diabetic subjects, postprandial insulin, apolipoprotein B, and LDL triglycerides were found to be the main determinants of IMT (21). In nondiabetic individuals, IMT was shown to be associated with age, male sex, total cholesterol, and smoking (14,36,37). In a previously published work (26) on IMT in nondiabetic subjects, we found, similarly, that age, male sex, and total and HDL cholesterol were independent determinants of intimal-medial thickening. Postprandial plasma glucose was also shown to be a significant risk factor for IMT in nondiabetic subjects (27). In the present study, after age and sex adjustment, the 2-h plasma glucose level in OGTT was significantly correlated to IMT in the total group, but not in the diabetic or control groups when analyzed separately. It is beyond the scope of the present article to clarify the correlations of IMT in the different stages of glucose tolerance; however, it is evident that if subjects with normal glucose tolerance are analyzed separately, albuminuria, total-to-HDL cholesterol ratio, and triglycerides are significantly positively correlated to IMT, and HDL cholesterol is inversely correlated to IMT, after adjustment for age and sex. The fact that in multivariate analysis no independent determinants of carotid IMT were found in the diabetic group could indicate that diabetes itself might be of crucial importance for the development of atherosclerosis because of the clustering of various interrelated metabolic disturbances. Thus, in our study, and consistent with previous publications (38,39), only 2 out of 71 diabetic subjects had no other standard risk factor for atherosclerosis, whereas the majority of patients displayed a combination of diabetes with at least two other additional risk factors. Furthermore, a tendency was seen that the higher the number of risk factors, the thicker the intima-media. These data are compatible with the literature showing a distinct escalation of CHD mortality rates for the combination of several atherosclerosis risk factors (35,40). Since the relatively small number of subjects studied was a limitation for the application of sophisticated analytical methods in the present study, further investigations in that respect in larger populations will be necessary.

In conclusion, our data show that newly detected type 2 diabetic patients exhibit a higher degree of early atherosclerosis than normal glucose tolerance subjects matched for age and sex, suggesting that hyperglycemia together with a clustering of risk factors, particularly dyslipidemia, may cause intimal-medial thickening in the early phases of diabetes.

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