

Impaired Coronary Endothelium-Dependent Vasodilation Is Associated With Microalbuminuria in Patients With Type 2 Diabetes and Angiographically Normal Coronary Arteries

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OBJECTIVE— Microalbuminuria and impaired endothelium-dependent vasodilation are both predictors for cardiac events in patients with type 2 diabetes. The aim of the study was to evaluate whether microalbuminuria correlated with coronary endothelium-dependent vasodilation.

RESEARCH DESIGN AND METHODS— We evaluated 84 patients (47 men, mean age 50.5 ± 5.9 years) with type 2 diabetes for 9.4 ± 3.4 years, without angiographic coronary stenosis and without major cardiovascular risk factors or other confounding factors, for endothelium investigation. Quantitative coronary angiography was used to assess coronary artery response to cold pressor testing, used to assess endothelium-dependent vasodilation, and to isosorbide dinitrate (endothelium-independent vasodilation).

RESULTS— Endothelium-dependent vasodilation differed in the patients with and without microalbuminuria (changes in coronary artery diameter during cold pressor testing: $-15.0 \pm 1.9\%$ vs. $-10.2 \pm 1.3\%$, respectively, $P < 0.05$) and correlated with urinary albumin excretion rate ($r = -0.39$, $P = 0.003$), diastolic blood pressure ($r = 0.29$, $P < 0.01$), and left ventricular mass index ($r = -0.24$, $P < 0.05$). Independent predictors for endothelium-dependent vasodilation were urinary albumin excretion rate ($\beta -0.04$ [95% CI -0.07 to -0.01], $P < 0.005$) and left ventricular mass index (-0.26 [-0.49 to -0.05], $P < 0.05$). Endothelium-independent vasodilation was similar in both groups.

CONCLUSIONS— Type 2 diabetic patients with microalbuminuria have a more severely impaired coronary endothelium-dependent vasodilation than those with normoalbuminuria. These data suggest a common pathophysiological process for both coronary vasomotor abnormalities and microalbuminuria.

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The high cardiovascular morbidity and mortality rates in the type 2 diabetic subjects are not entirely explained by the clustering of cardiovascular risk factors these patients exhibit (1). New indicators, such as urinary albumin excretion rate and endothelial dysfunction, may be involved. Microalbuminuria

is considered to be a marker of nephropathy in diabetes. More recently, its role as a cardiovascular risk marker has been highlighted in diabetic (1) and general (2) populations. Furthermore, it has been described as the strongest independent predictor of 11-year cardiovascular mortality in the Casale Monferrato Study (3). Because there is no plausible mechanism directly linking atherothrombotic disease to the urinary albumin loss, endothelial dysfunction has been suggested to be, at least partly, the pathophysiological process that causes both increased renal albumin loss and coronary artery disease. Endothelial dysfunction occurs early in the atherosclerotic process (4). Coronary endothelial dysfunction has been recently reported to predict cardiovascular events in type 2 diabetic patients with angiographically normal coronary arteries (5) as well as in the nondiabetic population (6).

Up to now, only peripheral flow-mediated vasodilation has been used to compare endothelial function in diabetic patients with or without microalbuminuria. Impaired brachial flow-mediated vasodilation has been demonstrated to be associated with microalbuminuria in type 2 diabetes (7). Using pharmacological (acetylcholine) or physiological (cold pressor) testing, coronary endothelial dysfunction has been demonstrated both in large vessels (coronary artery diameter variations) and in the microcirculation (blood flow changes) in type 2 diabetic patients (5,8,9). The aim of the present study was to compare epicardial coronary endothelial function in patients with type 2 diabetes according to the presence or absence of microalbuminuria.

RESEARCH DESIGN AND METHODS

Type 2 diabetic patients, who underwent a coronary angiography in our center between October

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Abbreviations: LAD, left anterior descending.

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

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1994 and May 2000 because of symptoms suggestive of angina and/or abnormal treadmill exercise testing or single-photon emission computed tomography combined with a stress exercise testing, were included by two experienced investigators.

Criteria of noninclusion were as follows: insulin treatment, arterial hypertension, total cholesterol serum level (without treatment or with lipid-lowering therapy) >5.70 mmol/l (220 mg/dl) or LDL cholesterol >3.70 mmol/l (143 mg/dl), smoking, obesity (BMI ≥ 30 kg/m²), family history of premature coronary artery disease (defined as a first-degree relative aged <60 years with clinical evidence of coronary atherosclerosis), age >65 years, and postmenopausal women with substitutive hormonal therapy. Patients with history of myocardial infarction, unstable angina, heart failure, valvular heart disease, and atrial fibrillation were also excluded.

The study protocol was approved by an institutional ethical review committee. It was proposed to the patients the day before the angiographic exploration. A written consent was obtained from the subjects after the nature of the procedure was explained, and patients were informed that the procedure will be performed only if coronary arteries were angiographically normal.

Laboratory measurements

The following measurements were recorded on the same day: HbA_{1c} (agarose electrophoresis; normal value $<6\%$; Hy-ris Hydrasys, Sebia, France); serum total cholesterol, HDL cholesterol, and triglycerides (enzymatic colorimetry; Hitachi 912; Roche Diagnostic); creatininemia (colorimetry; Kone Optima; Thermolab Systems, Helsinki, Finland); and urinary albumin excretion rate on a 24-h urine collection (laser immunonephelometry; BN100; Dade-Behring, Paris, France). LDL cholesterol was calculated according to the Friedwald formula and creatinine clearance according to the Cockcroft and Gault formula.

Echocardiographic measurements

Left ventricular dimensions, mass, and systolic function were assessed by two-dimensional and M mode echocardiography. Left ventricular mass was estimated according to Penn convention and indexed for body surface area (10).

Table 1—Baseline clinical and biochemical characteristics of the patients

	All patients	Patients with microalbuminuria	Patient without microalbuminuria
<i>n</i>	84	25	59
Age (years)	50.5 \pm 5.9	51.2 \pm 5.7	50.3 \pm 6.0
Sex (male/female)	47/37	12/13	35/24
Diabetes duration (years)	9.4 \pm 3.9	9.6 \pm 2.7	9.3 \pm 2.7
Neuropathy	19 (22.6)	7 (28.0)	12 (20.3)
Retinopathy	27 (32.1)	9 (36.0)	18 (30.5)
HbA _{1c} (%)	6.7 \pm 0.9	6.7 \pm 0.9	6.7 \pm 0.9
BMI (kg/m ²)	27.2 \pm 1.6	27.2 \pm 1.7	27.2 \pm 1.6
Creatinine clearance (ml/min)	115.7 \pm 17.0	118.2 \pm 17.0	114.6 \pm 17.0
Albumin excretion rate (mg/24h)	59.9 \pm 75.2	155.5 \pm 76.9*	19.4 \pm 5.3
Total cholesterol (mmol/l)	5.02 \pm 0.26	4.94 \pm 0.21	5.05 \pm 0.27
Triglycerides (mmol/l)	1.30 \pm 0.16	1.29 \pm 0.15	1.31 \pm 0.17
HDL cholesterol (mmol/l)	1.58 \pm 0.17	1.58 \pm 0.18	1.58 \pm 0.17
LDL cholesterol (mmol/l)	3.17 \pm 0.29	3.09 \pm 0.26	3.20 \pm 0.30
Systolic blood pressure (mmHg)	131.4 \pm 5.2	131.9 \pm 5.3	131.2 \pm 5.3
Diastolic blood pressure (mmHg)	81.9 \pm 4.7	80.1 \pm 4.9†	82.7 \pm 4.4
Ejection fraction (%)	60.9 \pm 3.7	60.2 \pm 4.2	61.2 \pm 3.5
Left ventricular mass index (g/m ²)	90.4 \pm 9.9	92.7 \pm 8.9	89.4 \pm 10.2
Treatment			
Lipid-lowering therapy	33 (39.3)	14 (56.0)	19 (32.2)
Sulfonylureas	32 (38.1)	10 (40.0)	22 (37.3)
Metformin	44 (52.4)	14 (56.0)	30 (50.8)
α -Glucosidase inhibitor	36 (42.9)	9 (36.0)	27 (45.8)

Data are means \pm SD or *n* (%). * $P < 0.0001$ comparing patients with and without microalbuminuria. † $P < 0.05$.

Measurement of coronary endothelium-dependent and -independent vasodilation

Patients were studied in the fasting state without premedication. Fifteen minutes after the diagnostic coronary arteriography, hemodynamic measurements (heart rate and aortic systolic and diastolic blood pressure) and a left anterior descending (LAD) coronary angiogram were recorded at baseline. Five minutes later, cold pres-

or testing was performed. The patient's hands were immersed in crushed ice for 120 s. The same hemodynamic parameters were recorded and another LAD coronary angiogram was performed immediately before removal of the hands from ice. At the end of the protocol, endothelium-independent coronary artery dilation was studied using an intracoronary bolus of 2 mg isosorbide dinitrate. Measurement of the LAD coronary artery

Table 2—Coronary artery diameters (in millimeters) during the procedure

	Baseline	Cold pressor testing	Isosorbide dinitrate
All type 2 diabetic patients			
All patients (<i>n</i> = 84)	3.49 \pm 0.49	3.08 \pm 0.71*	4.29 \pm 0.51*
Dilation or no change (<i>n</i> = 22)	3.47 \pm 0.43	3.53 \pm 0.46†	4.23 \pm 0.44‡
Constriction (<i>n</i> = 62)	3.51 \pm 0.53	2.93 \pm 0.49*	4.31 \pm 0.53*
Patients with microalbuminuria			
All patients (<i>n</i> = 25)	3.44 \pm 0.49	2.92 \pm 0.66†	4.26 \pm 0.58*
Dilation or no change (<i>n</i> = 4)	3.50 \pm 0.41	3.50 \pm 0.51	4.32 \pm 0.60*
Constriction (<i>n</i> = 21)	3.42 \pm 0.53	2.80 \pm 0.47*	4.27 \pm 0.53*
Patients without microalbuminuria			
All patients (<i>n</i> = 59)	3.51 \pm 0.51	3.14 \pm 0.69†	4.30 \pm 0.48*
Dilation or no change (<i>n</i> = 18)	3.47 \pm 0.44	3.55 \pm 0.53†	4.23 \pm 0.46*
Constriction (<i>n</i> = 41)	3.52 \pm 0.56	2.96 \pm 0.42*	4.32 \pm 0.51*

Data are means \pm SD. * $P < 0.001$ vs. baseline; † $P < 0.05$; ‡ $P < 0.01$.

diameter was performed by a previously validated technique (5,9). The accuracy of the technique was $3.6 \pm 0.5\%$ and the precision $2.4 \pm 0.9\%$. The maximum error between the actual and the calculated diameter was equal to $\pm 5.7\%$ ($R^2 = 0.994$). Each angiogram was analyzed at random without knowledge of the sequence (baseline, cold pressor testing, and isosorbide dinitrate).

Statistical analyses

All data are expressed as means \pm SD. Differences between the groups of patients for clinical and biological characteristics and basal hemodynamic parameters were analyzed by the nonparametric Mann-Whitney test. Changes in hemodynamic parameters during the cold pressor testing were analyzed with paired Student's *t* test. Comparisons between coronary artery dimensions at baseline, during cold pressor testing, and after intracoronary isosorbide dinitrate were made by two-way ANOVA with repeated measures for experimental condition factor followed by the Fisher protected least-significance difference test. The Spearman test was used to find the correlates of coronary endothelium-dependent vasoreactivity. Due to its skewed distribution, urinary albumin excretion rate was log transformed in the correlation analyses. A backward linear multiple regression was performed to find the independent predictors for endothelium-dependent coronary vasoreactivity. Statistical significance was assumed when $P < 0.05$.

RESULTS

Baseline characteristics

Eighty-four patients were included in the study. Baseline clinical and biochemical characteristics of the patients are summarized in Table 1. Mean age was 50.5 ± 5.9 years and duration of diabetes 9.4 ± 3.2 years. Twenty-five patients had microalbuminuria defined as an albumin excretion rate of 30–300 mg/24 h. The patients with and without microalbuminuria were similar with regard to clinical and biochemical parameters, except for diastolic blood pressure, which was slightly but significantly lower in those with microalbuminuria (Table 1). Left ventricular mass index was also similar in the two groups. Left ventricular dimensions and systolic function were normal in all the patients. A total of 15 patients were treated with sulfonylureas, 16 with metformin, 25 with the α -glucosidase inhib-

Table 3—Hemodynamic data during the CPT: comparison between patients who constricted the LAD coronary artery and those who did not and between the patients without or with microalbuminuria

	All patients		Patients with dilation or no change		Patients with constriction		Patients without microalbuminuria		Patients with microalbuminuria	
	Baseline	CPT	Baseline	CPT	Baseline	CPT	Baseline	CPT	Baseline	CPT
<i>n</i>	84		22		62		59		25	
Heart rate (bpm)	76.2 \pm 10.8	79.3 \pm 11.1*	75.9 \pm 9.5	78.3 \pm 10.2†	76.4 \pm 11.3	79.5 \pm 12.6*	77.4 \pm 10.8	80.3 \pm 9.6*	73.5 \pm 10.7	77.1 \pm 11.5*
Aortic systolic blood pressure (mmHg)	131.4 \pm 5.2	163.4 \pm 12.6*	131.3 \pm 5.9	161.8 \pm 11.7*	131.4 \pm 5.1	164.3 \pm 13.1*	131.2 \pm 5.3	161.6 \pm 13.8*	131.9 \pm 5.3	165.4 \pm 11.8*
Rate \times pressure product (bpm \cdot mmHg ⁻¹ \cdot 10 ⁻²)	100.2 \pm 15.2	129.6 \pm 18.4*	99.6 \pm 13.1	126.7 \pm 19.6*	100.4 \pm 15.9	131.6 \pm 19.4*	101.5 \pm 15.8	129.8 \pm 17.2*	96.9 \pm 16.3	127.5 \pm 13.6*
Variation in rate \times pressure product (bpm \cdot mmHg ⁻¹ \cdot 10 ⁻²)	29.4 \pm 17.7		27.1 \pm 18.5		31.2 \pm 18.7		28.3 \pm 19.0		30.6 \pm 17.4	

Data are means \pm SD. * $P < 0.001$ vs. baseline; † $P < 0.01$. CPT, cold pressor testing.

itor acarbose, 17 with sulfonylureas and metformin, and 11 with metformin and acarbose.

Epicardial coronary artery responses to the cold pressor testing and isosorbide dinitrate

Due to the highest error reported in the validation technique for the quantification method of coronary artery diameter (5.7%), a change in the diameter of the LAD coronary artery was defined as a minimal 6% variation. Therefore, two patterns of responses were identified: one defined by a dilation (change $\geq +6\%$) or no change (between -6 and $+6\%$) and the other by a constriction (change $\geq -6\%$) of LAD coronary artery.

The coronary artery diameters throughout the procedure are shown in Table 2. Among 84 patients, 62 (73.8%) constricted, whereas 22 (26.2%) had no change ($n = 17$) or dilated ($n = 5$) their LAD coronary artery. The changes of the LAD artery diameter at the end of the cold pressor testing were significantly lower in the patients with ($-15.1 \pm 1.9\%$) than in those without ($-10.2 \pm 1.3\%$) microalbuminuria ($P < 0.05$). During the cold pressor testing, heart rate, systolic aortic pressure, and the heart rate \times pressure product similarly increased in both groups (Table 3). Endothelium-independent LAD coronary artery dilation to isosorbide dinitrate was similar in the patients with and without microalbuminuria (Table 2).

Parameters associated with endothelium-dependent coronary vasoreactivity

Univariate analysis showed that endothelium-dependent vasoreactivity correlated with urinary albumin excretion rate ($r = -0.39$, $P = 0.0003$, Fig. 1), diastolic blood pressure ($r = 0.29$, $P = 0.007$), and left ventricular mass index ($r = -0.24$, $P = 0.026$). Independent predictors of endothelium-dependent vasoreactivity were urinary albumin excretion rate ($\beta -0.04$ [95% CI -0.07 to -0.01], $P < 0.005$) and left ventricular mass index (-0.26 [-0.49 to -0.05], $P < 0.05$).

CONCLUSIONS— There is increasing evidence that patients with type 2 diabetes exhibit impaired endothelium-dependent vasodilation compared with nondiabetic subjects (11–13). Coronary and peripheral endothelial dysfunctions have a similar power to predict major cardiac events, as recently reviewed (6). Mi-

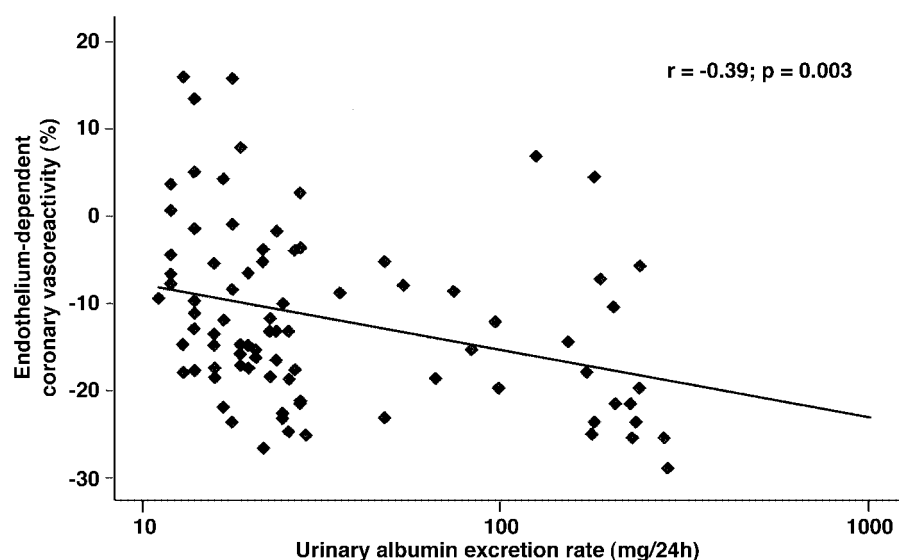


Figure 1—Correlation between endothelium-dependent coronary vasoreactivity, determined as coronary artery diameter change after the cold pressor testing (%), and urinary albumin excretion rate.

croalbuminuria has also been reported to be associated with a poor cardiovascular prognosis (1,14). In the present study, we demonstrated for the first time, in the type 2 diabetic population, that patients with microalbuminuria have a significantly more severe impairment of coronary endothelium-dependent vasodilation compared with the patients without microalbuminuria. In contrast, endothelium-independent vasodilation did not differ in normo- and microalbuminuric patients. However, the association between urinary albumin excretion rate and endothelium-dependent coronary diameter changes during the cold pressor testing was low ($r = -0.39$) and thus only partly explains shared phenomena of both conditions in the type 2 diabetic population. Correlations between C-reactive protein and microalbuminuria (7) and with impaired endothelial vasoreactivity (15) have been reported. Thus, a systemic inflammation might also be associated with coronary endothelial dysfunction. Others factors might be involved, such as an increase in free fatty acid levels, since they were reported to induce endothelium-dependent dysfunction (16).

Coronary and peripheral endothelial dysfunction and microalbuminuria

Whether microalbuminuria is associated with a more severely impaired conduit artery endothelium function in type 2 diabetes is not well established. However, in line with our results, the presence of mi-

croalbuminuria has been reported to be associated with biochemical indexes of endothelial dysfunction, such as an increase in serum levels of von Willebrand factor, endothelin, tissue plasminogen activator, and fibrinogen (17). Interestingly, Papaioannou et al. (7) have recently reported in a series of type 2 diabetic patients enrolled in the Detection of Ischemia in Asymptomatic Diabetics study that brachial flow- and endothelium-dependent vasodilation was impaired in the patients with microalbuminuria compared with the patients with normal albuminuria. Furthermore, peripheral endothelial dysfunction has been shown to correlate with peripheral insulin resistance and microalbuminuria in patients with type 2 diabetes (12). In these studies, brachial artery reactivity but not coronary endothelium function was explored. However, it has been suggested that conduit artery endothelial dysfunction roughly correlated ($r = 0.36$, $n = 50$) with abnormal vasomotor responses of the coronary circulation (18).

Other risk factors and endothelial dysfunction

Patients with type 2 diabetes often have additional risk factors that may participate to endothelial dysfunction. Those components of the metabolic syndrome (19), such as high blood pressure (4,13), dyslipidemia (13), and obesity (13), have all been reported to correlate with coronary endothelial function and also with urinary albumin excretion rate (20).

Other potential confounding factors include the age and sex of the population (21), smoking habits (13,22), glycemic control (13), and concurrent medication, especially antihypertensive (13), lipid-lowering (13,23), and hormone replacement (24) therapies. To avoid such factors, which could have been limitations to the present study, we selected a population of patients with type 2 diabetes free of other major cardiovascular risk factors. However, the levels of lipid parameters were slightly over the present recommended goals (25) but correspond to the recommendations at the time of inclusion for the first patients. Moreover, the patients with and without microalbuminuria were similar, especially with regard to sex ratio, age, diabetes duration, glycemic control, BMI, serum lipid levels, and treatment. Therefore, the more severe coronary vasoconstriction in the patients with microalbuminuria cannot be explained by a different metabolic status.

Endothelium-independent coronary vasodilation

Because coronary artery diameter changes in response to an exogenous donor of nitric oxide, isosorbide dinitrate, were similar in the patients with or without microalbuminuria, an impaired responsiveness of underlying vascular smooth muscle cells or structural changes of the vascular wall can also be ruled out. Concerning smooth muscle cell function and coronary endothelium-independent vasodilation, Papaioannou et al. (7) have reported abnormal responses in the brachial artery of type 2 diabetic patients, which are also at variance with our findings. This discrepancy could be due to differences in patient characteristics, the different techniques used to assess smooth muscle cell function, and different responses through the artery territories. In addition, it should be pointed out that our patients were younger, with a shorter duration of diabetes, at a lower risk, and were receiving fewer medications at the time of investigations. Furthermore, they had no associated major risk factor that might have influenced the results.

Methodological considerations

In normal subjects, the cold pressor testing induces sympathetic activation, thus increasing heart rate, arterial blood pressure, and myocardial oxygen demand. Enhanced myocardial demand results in an increase in coronary blood flow and

flow-dependent dilation of epicardial coronary arteries. Paradoxical coronary vasoconstriction during this test is an index of local endothelial dysfunction (26). It has been described in patients with type 2 diabetes in a similar proportion (~70%) as in the present series and more frequently than in control subjects (5,9). We cannot exclude angiographically undetectable atherosclerosis in our patients, since intravascular ultrasound studies have shown that early coronary atherosclerosis can be present despite angiographically normal vessels (27). However, it has been shown that there was no significant correlation between coronary intravascular ultrasound results and endothelium-dependent response to acetylcholine (28). Lastly, the results show that baseline and the maximal diameter of the coronary arteries were similar in the patients with or without microalbuminuria. Therefore, we think that concentric diffuse coronary atherosclerosis can reasonably be ruled out.

Conclusion

Our results strongly suggest that coronary endothelial dysfunction correlates with increasing levels of urinary albumin excretion rate in patients with type 2 diabetes. The ubiquity of endothelium dysfunction, but most of all its localization in the coronary network, is likely to play a major part in the increased cardiovascular risk related to microalbuminuria. The pathophysiological relationship between microalbuminuria and coronary endothelium dysfunction and the clinical relevance of their combined effect on cardiovascular risk remain to be clarified. Various treatments may decrease albumin excretion rate and reverse endothelial dysfunction. Lipid-lowering agents, such as statins (23,29) and fibrates (30), and antihypertensive therapies, including ACE inhibitors, angiotensin II receptor antagonists, and calcium channel blockers (31), have demonstrated such effects and might be beneficial to the patients with both disorders. Whether the combination of several of these drugs may synergistically act on both renal protection and endothelium function in patients with microalbuminuria remains to be evaluated. Assessing the response to the cold pressor testing during a coronary angiography is safe, not very time consuming, and relatively easy. Future testing of the efficacy of a pharmacological treatment on coronary endothelium dysfunction, in particular in diabetic patients with mi-

croalbuminuria, might be helpful to predict its long-term efficacy in the prevention of cardiovascular events.

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