Kidney International, Vol. 66, Supplement 92 (2004), pp. S42–S44

Microalbuminuria is associated with impaired brachial artery, flow-mediated vasodilation in elderly individuals without and with diabetes: Further evidence for a link between microalbuminuria and endothelial dysfunction—The Hoorn Study

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Microalbuminuria is associated with impaired brachial artery, flow-mediated vasodilation in elderly individuals without and with diabetes: Further evidence for a link between microalbuminuria and endothelial dysfunction—The Hoorn Study.

Background. Extensive endothelial dysfunction (i.e., affecting many aspects of endothelial function) has been hypothesized to explain why microalbuminuria (MA) is associated with cardiovascular disease risk. However, it is not clear whether MA is specifically associated with impaired endothelial nitric oxide (NO) synthesis in individuals without and with type 2 diabetes.

Methods. We did a population-based study in 645 individuals (mean age 68 years; 248 with normal glucose metabolism, 137 with impaired glucose metabolism, and 260 with type 2 diabetes) and investigated associations of MA [present (urinary albumin-creatinine ratio ≥2 mg/mmol) versus absent, and in four categories (<2, ≥2 to 5, ≥5 to 10, ≥10 mg/mmol)] with ultrasonically measured brachial artery endothelium-dependent, flow-mediated (FMD; an estimate of endothelial NO synthesis) and endothelium-independent, nitroglycerin-induced vasodilation (NID).

Results. FMD was 0.12 mm in the presence of MA ($N = 93$; 49 with diabetes), and 0.18 in its absence ($P = 0.002$). After adjustment for age, sex, baseline arterial diameter, and other potential confounders, FMD was 0.038 mm (95% CI, 0.001 to 0.075) lower in the presence of MA ($P = 0.04$), and decreased linearly across MA categories [by 0.027 mm (0.007 to 0.046) per category increase of MA; $P = 0.007$]. NID was similar in individuals with and without MA. Results were similar in individuals without and with diabetes.

Conclusion. Microalbuminuria is linearly associated with impaired endothelium-dependent, flow-mediated vasodilation in elderly individuals without and with diabetes. These findings support the concept that impaired endothelial nitric oxide synthesis plays a role in the association of microalbuminuria with cardiovascular disease risk.

Key words: albumin excretion, endothelium, cardiovascular disease, diabetes.

In diabetes, much of the disease burden occurs in patients with diabetic nephropathy because they have the highest chance of developing not only renal failure, but also cardiovascular disease, severe retinopathy, and severe neuropathy. The association between renal and cardiovascular disease is seen even in individuals with early nephropathy [microalbuminuria (MA)], and exists regardless of the presence of diabetes. One hypothesis to explain the link between MA and cardiovascular disease is that extensive endothelial dysfunction (ED) represents the common antecedent to both.

ED can be defined as any change in endothelial properties that is inappropriate with regard to the preservation of organ function. Therefore, many types of ED exist, depending on which function is affected (e.g., the regulation of hemostasis and fibrinolysis, vasomotor activity, permeability to macromolecules, leukocyte adhesion, or vascular smooth muscle cell proliferation). Nitric oxide (NO) is a particularly important endothelium-derived mediator because of its vasodilator, anti-platelet, anti-proliferative, anti-adhesive, permeability-decreasing, and anti-inflammatory properties. Generalized ED (i.e., affecting many functions) is now considered a transducer of atherogenic risk factors, and is thought to play an important role both in the initiation and the progression of atherosclerosis. Therefore, an association of MA with generalized ED, if it exists, could explain the fact that MA strongly predicts cardiovascular disease.

MA in type 1 and 2 diabetes is usually [1, 2], but perhaps not always [2], accompanied by ED with regard to the regulation of hemostasis, fibrinolysis, leukocyte adhesion, and NO synthesis and/or availability (i.e., ED is, at the very least, extensive). Whether this occurs in all

vascular beds is extremely difficult to test in humans, but is obviously an important question. There are fewer data on the extent of ED in nondiabetic individuals with MA, but such ED has, as in diabetes, been suggested to involve the regulation of hemostasis, fibrinolysis, and leukocyte adhesion [2–5]. However, it is controversial whether NO synthesis and/or availability are impaired in nondiabetic individuals with MA [5–7].

To investigate this issue more fully, we examined brachial artery, flow-mediated vasodilation (FMD; an estimate of endothelium-derived NO synthesis) in elderly individuals without and with MA in the population-based Hoorn Study.

METHODS

The population has been described in detail elsewhere [8, 9]. MA was defined as urinary albumin-creatinine ratio (ACR) ≥2 mg/mmol (based on a single first-voided morning urine sample). FMD and nitroglycerin-induced, endothelium-independent dilation (NID) were measured by ultrasound as described elsewhere [9, 10]. We used multivariate linear regression to analyze associations of MA [present vs. absent and in four categories (<2, ≥2 to 5, ≥5 to 10, ≥10 mg/mmol)] with FMD and NID.

RESULTS

Table 1 shows the characteristics of the study population. Ninety-three individuals had MA (49 with diabetes; 53, 20, and 20 with ACR ≥2 to 5, ≥5 to 10, and ≥10 mg/mmol, respectively). FMD was 0.12 mm in the presence of MA and 0.18 in its absence ($P = 0.002$; Table 2). After adjustment for age, sex, baseline arterial diameter, and increase in peak systolic velocity, FMD was 0.038 mm (95% CI, 0.001 to 0.075) lower in the presence of MA ($P = 0.04$) and decreased linearly across MA categories [by 0.027 mm (0.007 to 0.046) per category increase of MA; $P = 0.007$; Table 3, model 3]. Additional adjustments did not materially affect these results (Table 3, models 4–11). NID was similar in individuals with and without MA. All results were similar in individuals without and with diabetes [P for interaction of diabetes with MA in model 5 of Table 3 = 0.9 (dichotomized) and = 0.62 (in categories), respectively], and whether or not individuals with ACR >30 mg/mmol ($N = 4$) were excluded.

Table 1. Characteristics of the study population according to the presence or absence of microalbuminuria

	Micro-albuminuria present	Micro-albuminuria absent	P value
Number (men/women)	93 (55/38)	552 (265/287)	–
Age *years*	70 ± 8	67 ± 4	.006
Blood pressure *mm Hg*	151 ± 18/81 ± 10	141 ± 19/76 ± 9	<.001/<.001
Hypertension %	82	66	<.001
Antihypertensive medication %	48	33	<.001
Total cholesterol *mmol/L*	5.5 ± 1.1	5.8 ± 1.0	.02
HDL cholesterol *mmol/L*	1.3 ± 0.4	1.4 ± 0.4	0.50
LDL cholesterol *mmol/L*	3.4 ± 0.9	3.7 ± 0.9	0.25
Triglycerides *mmol/L*	1.4 (1.1–1.9)	1.4 (1.0–1.9)	.51
Lipid-lowering medication %	22	15	<.001
Body mass index kg/m^2	28 ± 4	27 ± 4	.49
Waist-to-hip ratio	0.95 ± 0.09	0.92 ± 0.10	.01
Smoking %	22	14	.048
Prior cardiovascular disease %	64	44	<.001
Serum creatinine *μmol/L*	100 ± 25	93 ± 14	<.001
NGM/IGM/DM-2 *N*	22/22/49	226/115/211	–

Abbreviations are: NGM, normal glucose metabolism; IGM, impaired glucose metabolism; DM-2, type 2 diabetes. Results are mean ± standard deviation or median (interquartile range).

Table 2. Brachial arterial properties according to the presence or absence of microalbuminuria

	Micro-albuminuria present	Micro-albuminuria Absent	P value
Diameter *mm*			
Baseline diameter	4.87 ± 0.80	4.64 ± 0.74	.006
After endothelium-dependent dilation	4.98 ± 0.80	4.81 ± 0.73	.04
After endothelium-independent dilation	5.28 ± 0.80	5.08 ± 0.73	.02
Absolute change in diameter *mm*			
After endothelium-dependent dilation	0.12 ± 0.13	0.18 ± 0.17	.002
After endothelium-independent dilation	0.42 ± 0.23	0.45 ± 0.23	.12
Peak systolic velocity *cm/s*			
At baseline	61 ± 12	58 ± 13	.02
After endothelium-dependent dilation	106 ± 26	106 ± 26	.96
Percentage increase from baseline	76 ± 42	87 ± 43	.02

DISCUSSION

The major new finding of this population-based study is that FMD is impaired in elderly individuals with MA whether or not they have type 2 diabetes. Together with previous data [3–6], this supports the concept that ED is extensive even in nondiabetic individuals with MA and that such extensive ED, including impaired endothelial nitric oxide synthesis and/or availability, plays a role in the association of MA with cardiovascular disease risk in nondiabetic individuals.

It must be emphasized that prospective studies are needed to test whether ED actually explains the link between MA and cardiovascular disease. Of three previous studies that used plasma markers of ED [4, 11, 12], two

Table 3. Flow-mediated, endothelium-dependent vasodilation (absolute change in diameter) and microalbuminuria: Adjusted analyses

Model	Microalbuminuria yes vs. no β (95% CI)	*P* value	Microalbuminuria categories β (95% CI)[a]	*P* trend for categories of microalbuminuria[a]
1. (Micro-)albuminuria	−0.058 (−0.096 to −0.022)	<.001	−0.035 (−0.055 to −0.015)	.001
2. 1 + baseline diameter + % increase in peak systolic velocity	−0.044 (−0.082 to −0.007)	.02	−0.028 (−0.048 to −0.008)	.007
3. 2 + sex + age	−0.038 (−0.075 to −0.001)	.04	−0.027 (−0.046 to −0.007)	.007
4. 3 + hypertension[b]	−0.034 (−0.071 to 0.003)	.07	−0.025 (−0.045 to −0.006)	.01
5. 3 + glucose tolerance status	−0.038 (−0.067 to 0.006)	.10	−0.022 (−0.041 to −0.002)	.03
6. 3 + body mass index	−0.037 (−0.074 to −0.001)	.05	−0.026 (−0.046 to −0.007)	.008
7. 3 + waist-to- hip ratio	−0.035 (−0.072 to 0.002)	.06	−0.025 (−0.045 to −0.005)	.01
8. 3 + smoking	−0.031 (−0.068 to 0.005)	.09	−0.023 (−0.042 to −0.003)	.02
9. 3 + prior cardiovascular disease	−0.028 (−0.066 to 0.009)	.14	−0.020 (−0.042 to −0.002)	.03
10. 3 + serum creatinine	−0.041 (−0.078 to −0.005)	.03	−0.031 (−0.050 to −0.011)	.003
11. 3 + total cholesterol[c]	−0.037 (−0.074 to −0.001)	.04	−0.027 (−0.046 to −0.007)	.008

[a] See **Methods**.
[b] Results were similar if hypertension was replaced by systolic, diastolic, pulse, or mean pressure, or the use of antihypertensive medication.
[c] Results were similar if total cholesterol was replaced by HDL cholesterol, LDL cholesterol, triglycerides, or the use of lipid-lowering medication.

[4, 11] found no strong evidence in favor of this hypothesis, which may mean that ED was not measured with sufficient precision, that the types of ED tested were irrelevant with regard to cardiovascular risk in MA, or that ED, although associated with MA, does not explain the MA-cardiovascular disease link.

Because ED precedes and predicts the onset of MA [3, 4, 11–13], it is tempting to postulate that ED causes MA. Alternatively, the association between ED and MA could be explained by a common antecedent that causes both, but the association persists when adjusted for common risk factors. Theoretically, ED could cause MA both directly by increasing glomerular pressure and glomerular basement membrane permeability, and indirectly by influencing mesangial cell and podocyte function in a paracrine fashion (e.g., through inflammatory mechanisms). Importantly, the molecular pathways by which ED causes MA have yet to be worked out [2].

CONCLUSION

ED in individuals with MA is usually extensive (i.e., affects many aspects of endothelial function) regardless of the presence of diabetes. The close linkage between MA and ED is an attractive but unproven explanation for the fact that MA is a risk marker for atherothrombosis. ED predicts the occurrence of MA, but whether this is causal has not been determined.

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