Cigarette Smoking Is Associated With Low Glomerular Filtration Rate in Male Patients With Type 2 Diabetes

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OBJECTIVE — The relationship between cigarette smoking and renal dysfunction in diabetes has predominantly been documented in patients with type 1 diabetes. The aim of the present study was to explore the relationship between cigarette smoking and glomerular filtration rate (GFR) in a large cross-sectional study carried out in male subjects with type 2 diabetes. The role of metabolic syndrome in modulating this relationship was also investigated.

RESEARCH DESIGN AND METHODS — One hundred fifty-eight current smokers and 158 never smokers with type 2 diabetes were consecutively recruited. Low GFR was defined as GFR <60 ml/min per 1.73 m^2.

RESULTS — The proportion of patients affected by low GFR was significantly higher in current smokers (20.9 vs. 12.0%, $P = 0.03$). The adjusted risk (odds ratio [OR]) of low GFR in current smokers was 2.20 (95% CI 1.14–4.26, $P = 0.02$) and markedly higher in patients from the first tertile of disease duration (4.27 [1.26–14.40], $P = 0.02$). When metabolic syndrome was added to the statistical model exploring the relationship between smoking and low GFR, the risk of low GFR showed a small change, although it did not become any more significant (1.84 [0.98–3.45], $P = 0.06$). Current smokers showed even higher free oxygen radical test unit values (560.0 ± 91.5 vs. 442.7 ± 87.2, $P < 0.0001$).

CONCLUSIONS — In a large population of male patients with type 2 diabetes, the risk of low GFR is markedly enhanced by smoking and is at least partially mediated by metabolic syndrome.

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Because of its detrimental clinical outcomes, including end-stage renal disease and cardiovascular mortality and morbidity, chronic kidney disease is a worldwide public health problem (1). Much evidence suggests that cigarette smoking is a strong and independent risk factor for kidney dysfunction in the general population and in diabetic patients (2–4). Whereas this relationship has been well established in patients with type 1 diabetes, studies in type 2 diabetes have been carried out only in small samples, so that conclusive data have not yet been obtained (5–9).

The major aim of the present study was to explore the relationship between cigarette smoking and glomerular filtration rate (GFR) in a large cross-sectional study comprising 316 males with type 2 diabetes. Because smoking, especially in men, induces insulin resistance/metabolic syndrome (10–12), which in turn has been reported to exert an adverse effect on kidney function in type 2 diabetes (13), we also investigated the role of metabolic syndrome in modulating this relationship.

RESEARCH DESIGN AND METHODS

— This study was conducted in Caucasian male patients with type 2 diabetes who were resident in Apulia, Southeast Italy. A total of 158 never smokers and 158 current smokers were consecutively recruited at the Unit of Endocrinology and Diabetology of the University of Foggia and at the Unit of Endocrinology of the CSS Scientific Institute in San Giovanni Rotondo. All patients were interviewed regarding duration of type 2 diabetes, diagnosis, and ongoing antidiabetic, hypolipidemic, and antihypertensive treatments. Duration of diabetes was calculated from the calendar year of data collection minus the calendar year of diabetes diagnosis. All subjects enrolled in the study underwent physical examination, including measurements of height, weight, waist circumference, and blood pressure (i.e., two measurements rounded to the nearest 2 mmHg in the sitting position after at least 5 min rest, using an appropriate-sized cuff; diastolic blood pressure was recorded at the disappearance of Korotkoff sound, phase V). Fasting venous blood was sampled from an antecubital vein from all patients to measure serum creatinine (standardized serum creatinine was measured by the modified kinetic Jaffé reaction), serum total cholesterol, HDL cholesterol, triglycerides, and GHb, as previously described (14) and to measure oxidative stress markers by the free oxygen radical test (FORT). The FORT (Incomat Medizinische Geräte) uses methods similar to those for determining reactive oxygen metabolites (15), and both the FORT (16) and the test for determining reactive oxygen metabolites (17) have been used by other investigators to assess oxidative stress levels in humans (15). Both intra-

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Abbreviations: ACR, albumin-to-creatinine ratio; e-GFR, estimated glomerular filtration rate; FORT, free oxygen radical test; GFR, glomerular filtration rate.

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

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Table 1—*Clinical features of 316 men with type 2 diabetes according to smoking status*

	Never smokers	Current Smokers
n	158	158
Age (years)	61.8 ± 9.7	61.4 ± 11.9
Duration of diabetes (years)	10.9 ± 9.6	11.8 ± 9.6
BMI (kg/m^2)	29.4 ± 5.3	28.4 ± 5.5
Waist circumference (cm)	101.2 ± 13.9	102.9 ± 15.9
Systolic blood pressure (mmHg)	133.4 ± 15.5	136.2 ± 17.9
Diastolic blood pressure (mmHg)	79.2 ± 8.4	79.4 ± 9.9
Triglycerides (mg/dl)	138 (43–1,824)	152 (20–711)
Total cholesterol (mg/dl)	189.6 ± 45.9	186.0 ± 45.0
HDL cholesterol (mg/dl)	41.6 ± 10.4	42.5 ± 14.3
GHb (%)	8.4 ± 2.0	9.1 ± 2.1†
ACR (mg/mmol)	1.36 (0.08–95.14)	2.06 (0.02–156.33)*
e-GFR (ml/min per 1.73 m^2)	81.6 ± 22.9	85.5 ± 29.3
Micro- and macroalbuminuria	61 (38.9)	76 (48.1)
Micro-/macroalbuminuria	52 (33.1)/9 (5.7)	61 (38.3)/15 (9.7)
FORT units	442.7 ± 87.2 (n = 54)	560.0 ± 91.5 (n = 46)†
Antidiabetic treatment		
Diet alone	17 (10.8)	15 (9.5)
OHA	82 (51.9)	84 (53.2)
Insulin ± OHA	59 (37.3)	59 (37.3)
Arterial hypertension	119 (75.3)	124 (78.5)
Treatment with ACE inhibitors/ARBs	61 (38.9)	92 (58.2)*
Dyslipidemia	129 (81.6)	131 (83.4)
Treatment with hypolipidemic therapy	41 (26.1)	55 (35.0)
Retinopathy	110 (69.9)	111 (70.7)
Low e-GFR	19 (12.0)	33 (20.9)*
Metabolic syndrome	109 (69.2)	120 (76.0)

Data are *n* (%), means ± SD, or median (range). *P* values for comparison between current smokers and never smokers: *$P < 0.05$; †$P < 0.0001$. ARB, angiotensin II receptor blocker; OHA, oral hypoglycemic agent.

and interassay coefficients of variation were <5%.

Urinary albumin and creatinine concentrations were determined on the morning of the clinical examination using an early morning first void sterile urine sample with the immunoturbidimetric and the Jaffé reaction-rate method, respectively. The urinary albumin-to-creatinine ratio (ACR) was then calculated. Microalbuminuria was diagnosed if the ACR was ≥2.5 mg/mmol but <30 mg/mmol. Macroalbuminuria was defined as an ACR ≥30 mg/mmol, a level that approximates an albumin excretion of 300 mg/24 h, considered as the upper limit of microalbuminuria (18). Estimated GFR (e-GFR) was calculated with the abbreviated modification of diet in renal disease formula (19). Low GFR was defined as e-GFR <60 ml/min per 1.73 m^2, a value that when recorded in the same patients for at least 3 months has been suggested as a cutoff for the definition of chronic kidney disease (20).

All patients were also interviewed regarding smoking habits. A current smoker was defined as an individual who had regularly smoked one or more cigarette a day for >1 year. A never smoker was a person who had never smoked. Median smoking index (mean daily number of cigarettes multiplied by years of smoking) was 375 (range 45.0–4000).

The diagnosis of metabolic syndrome was made using modified criteria proposed by the Third Report of the National Cholesterol Education Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults, as previously reported (21), and, in detail, patients were considered to have arterial hypertension if systolic blood pressure was ≥130 mmHg and diastolic blood pressure was ≥85 mmHg or they were currently receiving antihypertensive treatment. Patients were considered to have dyslipidemia if they were currently receiving lipid-lowering treatment or had total cholesterol ≥200 mg/dl, HDL cholesterol ≤40 mg/dl in men and 50 mg/dl in women, and triglycerides ≥150 mg/dl (22).

The presence of retinopathy was defined on funduscopy examination or as a history of laser therapy. The study was performed according to the Helsinki Declaration, and the protocol was approved by the local ethics committee. All subjects provided written informed consent.

Statistical analysis

Data are reported as means ± SD or median (range). Mean differences of normally distributed variables were compared by an unpaired Student's *t* test. In a multivariate logistic regression analysis, we explored the effect of independent variables (i.e., smoking status or presence/absence of metabolic syndrome, duration of disease, GHb, albuminuria, dyslipidemia, and LDL cholesterol) on the binary dependent variable (i.e., presence/absence of low e-GFR) and expressed as odds ratio (OR) (95% CI). For these analyses, skewed distributed variables (i.e., ACR and triglycerides) were logarithmically transformed. Statistical package SPSS version 11.5 (SPSS, Chicago, IL) was used. A *P* value <0.05 was considered to be significant.

RESULTS — Clinical features of patients according to smoking status are reported in Table 1. In the whole population, comprising current smokers and never smokers, the most important predictors of reduced e-GFR were arterial hypertension (OR 3.26 [95% CI 1.25–8.54], $P = 0.02$), albuminuria (3.15 [1.67–5.93], $P < 0.001$), metabolic syndrome (2.79 [1.20–6.45], $P = 0.02$), smoking habit (1.93 [1.04–3.57], $P = 0.04$), and duration of disease (1.03 [1.00–1.06], $P = 0.03$). Current smokers showed significantly higher ACR values than never smokers ($P < 0.05$) (Table 1) even though there was no difference in the frequency of patients with micro- and macroalbuminuria between the two groups. Compared with never smokers, the proportion of patients affected by low e-GFR was significantly higher among current smokers (20.9 vs. 12.0%; $P = 0.03$) with the risk of having low e-GFR being significantly increased in the latter group (2.20 [1.14–4.26], $P = 0.02$ after adjustment for duration of disease, GHb, albuminuria, and dyslipidemia) (Table 2). This result was unchanged if in the model the LDL cholesterol replaced dyslipidemia (2.04 [1.03–4.06], $P = 0.04$).

When the presence/absence of metabolic syndrome was also added into the model, the association between smoking habit and low e-GFR showed a small

Table 2—*Risk of having low e-GFR according to smoking status in 316 patients with type 2 diabetes*

	Low e-GFR		
	No	Yes	*P* value
Current smokers	125 (47.3)	33 (63.5)	
Never smokers	139 (52.7)	19 (36.5)	
OR			
Unadjusted	1.93 (1.04–3.57)		0.04
Adjusted*	2.20 (1.14–4.26)		0.02
Adjusted†	1.84 (0.98–3.45)		0.06

Data are *n* (%) or OR (95% CI). *Adjusted for duration of disease, GHb, albuminuria, and dyslipidemia. †Adjusted for duration of disease and presence/absence of metabolic syndrome.

change, although was no longer significant (Table 2). Of note, as previously reported (13), a significant association was also observed in the present population between metabolic syndrome and low e-GFR; in fact, among patients ($n = 52$) with low e-GFR, 45 (86.5%) had metabolic syndrome compared with 184 (69.7%) subjects who had metabolic syndrome among patients ($n = 264$) with e-GFR >60 ml/min per 1.73 m^2 ($P = 0.02$).

The effect of smoking on increasing the risk of low e-GFR was progressively reduced with increasing duration of diabetes, being highly significant in the first tertile of disease duration (0–6 years) (OR 4.27 [95% CI 1.26–14.40], $P = 0.02$ after adjusting for GHb) but no longer significant in the second (6.1–15 years) (1.41 [0.49–3.99], adjusted $P = 0.51$) and third (15.1–40 years) (1.70 [0.57–5.02], adjusted $P = 0.33$) tertiles. When patients with or without micro- or macroalbuminuria were analyzed separately, the effect of smoking was still significant in the former (2.95 [1.25–6.94], $P = 0.01$) but no longer significant in the latter group (1.07 [0.39–2.93], $P = 0.88$).

Because hyperfiltration is supposed to be an early manifestation of kidney disease in diabetes, we also compared the prevalence of patients with hyperfiltration (e-GFR >120 ml/min per 1.73m^2, which is the mean value of e-GFR plus 2 SD of the type 2 diabetes population in our centers with the same mean age) between current smokers and never smokers. Within the subgroup of patients with e-GFR ≥60 ml/min per 1.73 m^2, the frequency of hyperfiltration was higher in current smokers than in never smokers (19/125 [15.2%] vs. 8/139 [5.8%], $P = 0.01$).

To explore whether there was a relationship between the severity of kidney damage and the amount of cigarettes smoked per day, we performed a regression analysis in the whole population between e-GFR and the number of cigarettes smoked per day. The results were negative and probably due to an indication bias.

Finally, when FORT was performed on two subgroups of 46 current smokers and 54 never smokers randomly selected from the whole groups, significantly higher values were observed in current smokers (560.0 ± 91.5 vs. 442.7 ± 87.2 FORT units, $P < 0.0001$).

CONCLUSIONS — The main finding of this study is that male patients with type 2 diabetes who smoke are more frequently affected by low e-GFR. A similar association was reported by Briganti et al. (23) in men with high-normal systolic blood pressure or with high-normal 2-h glucose levels.

The association reported here in patients with type 2 diabetes is independent of age, GHb, albuminuria, and dyslipidemia and appears to be stronger in patients with a short duration of diabetes, thus suggesting that the deleterious effect of smoking is mainly responsible for earlier development of low e-GFR. By contrast, Chuahirun et al. (9) found in a small group of 84 patients with a recent diagnosis of type 2 diabetes that the effect of smoking was mediated by albuminuria.

Several mechanisms may have played a role in contributing to this association. Hyperfiltration is supposed to be an early manifestation of kidney disease in diabetes (24,25). Because our sample had a higher frequency of patients with hyperfiltration among current smokers, a previous condition of hyperfiltration could have contributed to the excess of low GFR detected in current smokers. The nicotine-induced increase in blood pressure and heart rate via sympathetic activation and vasopressin release (26) probably explains the higher frequency of hyperfiltration in our current smokers.

A growing body of evidence (10–12) indicates that tobacco smoke also causes metabolic syndrome, which is a risk factor of low e-GFR in patients with type 2 diabetes (13). Our data, in fact, suggest that the association between smoking and kidney function is only modestly mediated by metabolic syndrome as indicated by a very small loss of association between the two variables when the presence/absence of metabolic syndrome was added into the model. It is well known that current smokers also have a heightened state of oxidative stress, which is likely to play a role in inducing inflammation and endothelial dysfunction (27,28). As a matter of fact, in our sample, we were able to confirm that, compared with never smokers, diabetic patients who smoke have an increased level of oxidative stress, a mechanism that might be involved in the increased risk of low e-GFR in these patients.

It is worth knowing that in our population, a smoking habit is associated with increased urinary albumin excretion. This finding is in line with that reported by Gambaro et al. (8) who, in a retrospective study involving a small number of patients with type 2 diabetes, found that a smoking habit was independently associated with albuminuria and was an important predictor of diabetic nephropathy progression. However, no assessment of GFR was performed in their population. These observations are in contrast with those of Tung and Levib (29), who found a reduced risk of microalbuminuria among current smokers. Indeed this association was limited to a small proportion ($n = 67$) of patients, all of them receiving insulin treatment (29).

Because of the low smoking rate in our female population, women were not included in this study; thus, it is not known whether the association we observed between cigarette smoking and low GFR applies to both sexes. Information on socioeconomic condition, a variable reported to affect both kidney function and smoking habit, is unfortunately not available in our database and, therefore, has not been explored as a possible confounder in the model we tested.

In summary, this is the first evidence obtained in a large population indicating that, among male patients with type 2 diabetes, the risk of having low e-GFR is markedly heightened by cigarette smok-

ing. Although the cross-sectional design of our study does not allow drawing a firm conclusion about a cause and effect relationship, these data reinforce the hypothesis that cigarette smoking is a promoter of kidney damage in type 2 diabetes, as recently suggested by the beneficial effect of smoking cessation on renal injury (30). While waiting for prospective studies to better clarify the relationship between smoking and kidney damage in diabetic patients, efforts to help type 2 diabetic patients to quit smoking are strongly recommended.

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