

# Smoking Is Associated With Progression of Diabetic Nephropathy

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**OBJECTIVE**— To investigate the association between cigarette smoking and the progression of diabetic nephropathy.

**RESEARCH DESIGN AND METHODS**— A prospective, follow-up study over one year was conducted in a sequential sample of 34 smokers, 35 nonsmokers, and 24 ex-smokers with type I diabetes, hypertension, and diabetic nephropathy. Progression of renal disease was defined according to the stage of nephropathy as an increase in proteinuria or serum creatinine or a decrease in the glomerular filtration rate.

**RESULTS**— Progression of nephropathy was less common in nonsmokers (11%) than in smokers (53%) and patients who had quit smoking (33%),  $P < 0.001$ . In a stepwise logistic regression analysis, cigarette pack years, 24-h sodium excretion, and GHb were independent predictive factors for the progression of diabetic nephropathy. Because blood pressure (BP) was well controlled in these patients and most values were within a normotensive range, neither standing, sitting, nor supine BP values were associated with progression of nephropathy.

**CONCLUSIONS**— Cigarette smoking represents an important factor associated with progression of nephropathy in treated hypertensive type I diabetic patients.

The progression of diabetic nephropathy is delayed by antihypertensive therapy leading to an impressive improvement of the overall prognosis of diabetic renal disease (1).

The quality of metabolic control (2) and protein intake (3) also have influenced the deterioration of renal function in diabetic nephropathy. Cigarette smoking has been implicated in various patho-

physiological aspects of organ failure in late-onset diabetes complications (4). In several cross-sectional studies, smoking was clearly associated with diabetic nephropathy, whereas its effects on the course of diabetic nephropathy are unknown (5–7). In this prospective study, we present data on the progression of incipient and overt diabetic nephropathy in nonsmokers, smokers, and ex-smokers who were followed for one year under intensified insulin and antihypertensive therapy.

## RESEARCH DESIGN AND METHODS

The study group consisted of a consecutive sample of 96 hypertensive type I diabetic patients with diabetic nephropathy from the diabetic outpatient clinic of this department. All patients received antihypertensive drug therapy after confirmation of hypertension by multiple recordings of elevated blood pressure (BP) values ( $\geq 140/90$  mmHg) on different days. Before recruitment, all patients had participated in diabetes and hypertension treatment and teaching programs (8,9) to assure continuous good blood glucose and BP control. All patients performed multiple insulin injection therapy or continuous subcutaneous insulin infusion therapy including self-monitoring of blood glucose and self-adjustment of insulin dosages (8). After participation in the hypertension treatment and teaching program, all patients performed BP self-monitoring and adjusted their antihypertensive drug therapy (9). Of the patients, 3 died during the study period and were excluded from analysis. The remaining 93 patients were reexamined after one year according to a comprehensive protocol, which has been described in detail previously (9). Proteinuria was determined by laser-turbidimetry (10), and glomerular filtration rate (GFR) was determined by creatinine clearance (11). The diagnosis of diabetic nephropathy was established by persistent proteinuria after at least 6 years of diabetes duration and the pres-

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Type I diabetes, insulin-dependent diabetes mellitus; GFR, glomerular filtration rate; BP, blood pressure; sBP, systolic blood pressure; dBP, diastolic blood pressure; OR, odds ratio; BMI, body mass index; CI, confidence interval.

ence of diabetic retinopathy. Two hypertensive microproteinuric patients without retinopathy were not enrolled in the study because the lack of retinopathy might have indicated a different nondiabetic cause of microproteinuria. Incipient nephropathy was defined as protein excretion between 60 and 500 mg/24 h in at least three urine samples over 6 months and normal GFR (creatinine clearance  $>1.36 \text{ ml} \cdot \text{s}^{-1} \cdot 1.73\text{m}^{-2}$ ), whereas patients with reduction of GFR and/or proteinuria  $>500 \text{ mg/24 h}$  were regarded as having overt diabetic nephropathy (10,12).

Progression of nephropathy was defined in accordance with the stage of diabetic nephropathy by comparing a single baseline value of proteinuria, creatinine clearance, and serum creatinine with the respective value after one year of follow-up. In incipient nephropathy, an increase in proteinuria of  $>20\%$  and/or a pathological reduction of GFR  $<1.36 \text{ ml} \cdot \text{s}^{-1} \cdot 1.73\text{m}^{-2}$  with a decrease of  $>20\%$  were regarded as progression. In patients with overt nephropathy, changes in proteinuria were not taken into account. If serum creatinine was  $<160 \mu\text{M}$  in patients with overt nephropathy at baseline, progression was assumed when creatinine clearance was normal at baseline and pathological at follow-up (i.e.,  $<1.36 \text{ ml} \cdot \text{s}^{-1} \cdot 1.73\text{m}^{-2}$ ) with a decrease of  $>20\%$  and/or when serum creatinine was pathological at follow-up (i.e.,  $>120 \mu\text{M}$ ) and increased by  $>20\%$  during the study period. Changes in creatinine clearance within the normal values were not regarded as progression. In patients with overt nephropathy and advanced impairment in renal function (serum creatinine  $\geq 160 \mu\text{M}$  at baseline), changes in proteinuria and creatinine clearance alone were not taken into account. In these patients, only a further increase in serum creatinine of  $>20\%$  was regarded as progression.

HbA<sub>1c</sub> values were measured using the Diamat high-performance liquid chromatography analyzer (Bio-Rad, Mu-

nich, Germany) (normal range 4.2–5.5%). BP was measured by a specially trained paramedic with a Random-Zero sphygmomanometer (Hawksley and Sons, Sussex, England) at baseline and at final examination after a 10-min rest in supine position, after 1 and 3 min of standing, and after a 5-min rest in a sitting position. The mean of two supine measurements, and one measurement after 1 and 3 min of standing, respectively, and the mean of four sitting measurements were used for analysis. Sodium intake was estimated from sodium excretion, and protein intake was calculated from 24-h urinary urea nitrogen excretion in 24-h urine samples (13). Smoking history was assessed using a questionnaire, and data are presented as pack years. Ex-smokers were defined as subjects who reported having quit smoking before the baseline examination and were nonsmokers throughout the study. Two patients who had quit smoking during the study period were regarded as smokers. Nonsmokers were patients who described themselves as having never smoked.

### Statistical analysis

Statistical analysis was performed using Fisher's exact test for comparison of proportions, Wilcoxon's rank-sum test, and unpaired and paired Student's *t* tests for comparison of means.

Stepwise logistic regression analysis was used to examine the association between explanatory variables and the outcome variable progression of nephropathy. For regression analysis, the following baseline parameters were included as possible explanatory variables: age, sex, diabetes duration, stage of diabetic nephropathy, smoking status, cigarette pack years, duration of hypertension, height, serum creatinine, serum urea nitrogen, creatinine clearance, and proteinuria.

In addition, the following parameters were assessed both at baseline and at the follow-up examinations, and the differences of both were included in the

regression analysis: weight, total cholesterol, HDL cholesterol, HbA<sub>1c</sub>, daily insulin dosage, total serum protein, serum potassium, serum sodium, leukocyte count, number and kind of antihypertensive agents, daily protein intake, 24-h sodium excretion; and supine, standing, and sitting systolic blood pressure (sBP) and diastolic blood pressure (dBP) values. Maximum likelihood methods were used for parameter estimation, and Wald's  $\chi^2$  statistic was used for significance testing. These resulted in a ranking of explanatory variables according to their relative importance. Odds ratios (ORs) were obtained by exponentiating the estimated regression coefficients of significant risk factors multiplied by a specified difference. For computations, the SAS (Cary, NC) procedures PROC FREQ, PROC MEANS, PROC CORR, PROC TTEST, PROC NPAR1WAY, PROC CATMOD, and PROC LOGISTIC were used (14–16). Statistical significance was assumed at a 5% level. Unless otherwise indicated, two-tailed *P* values are given.

**RESULTS** — Patient characteristics are shown in Table 1. HbA<sub>1c</sub> values, body mass index, sodium excretion, and protein intake were not different between nonsmokers, ex-smokers, and smokers at any time. The groups did not differ with regard to supine, standing, or sitting sBP and dBP values, although a tendency toward lower BP values was detected among nonsmokers (Table 2).

Progression of nephropathy over one year was less common in nonsmokers ( $n = 4$ , 11%) than in smokers ( $n = 18$ , 53%),  $P < 0.001$ ; the differences between ex-smokers ( $n = 8$ , 33%) and smokers and ex-smokers and nonsmokers, respectively, were not statistically significant. Table 3 summarizes the renal parameters of the three patient groups as assessed at baseline and at follow-up. On separate analysis of patients in different stages of diabetic nephropathy, progression was less common among nonsmokers when compared with smokers both in incipient and in

Table 1—Characteristics of patients at baseline and at follow-up

	Nonsmokers	Ex-smokers	Smokers
n	35	24	34
F/M	20/15	8/16	17/17
Age (years)	35 ± 10	36 ± 8	36 ± 9
Diabetes duration (years)	21 ± 8	23 ± 8	21 ± 6
Cigarette pack years (n)	0	13 ± 11	18 ± 13
HbA <sub>1c</sub> (% total Hb)			
At baseline	7.8 ± 1.5	7.1 ± 1.2	8.0 ± 1.4
At follow-up	7.3 ± 0.9	7.2 ± 0.8	8.1 ± 1.5
BMI (kg/m <sup>2</sup> )			
At baseline	24.5 ± 3.1	25.9 ± 2.4	23.5 ± 3.5
At follow-up	24.8 ± 3.6	26.2 ± 1.9	23.4 ± 4.1
Sodium excretion (mmol/24 h)			
At baseline	168 ± 86	188 ± 97	182 ± 91
At follow-up	183 ± 85	170 ± 63	187 ± 76
Protein intake (g/kg body weight)			
At baseline	1.1 ± 0.4	0.9 ± 0.3	0.9 ± 0.3
At follow-up	0.9 ± 0.3	0.9 ± 0.3	0.8 ± 0.3

Data are means ± SD.

overt diabetic nephropathy (Table 3). Creatinine clearance decreased significantly only in smoking patients with overt nephropathy. In smokers with incipient nephropathy, a significant rise in creatinine clearance occurred. This phenomenon may be interpreted as a tendency to hyperfiltration in some of the

smoking patients in the early stage of nephropathy.

Table 4 shows how many patients had progression of nephropathy according to the various definitions used. Among smokers and ex-smokers, a positive correlation was found between the number of pack years and proteinuria at

follow-up (Spearman's rank correlation coefficient  $r = 0.37$ ,  $P = 0.0012$ ).

On subdivision of patients into those with and without progression of nephropathy, progressors had significantly more cigarette pack years ( $P = 0.001$ ) and higher HbA<sub>1c</sub> values ( $P = 0.026$ ), and a trend toward higher 24-h sodium excretion rates was observed in progressors at follow-up ( $P = 0.052$ ) (Table 5).

In the final logistic regression model using maximum likelihood estimation (14), pack years ( $P = 0.0004$ ), urinary sodium excretion at follow-up ( $P = 0.012$ ), and HbA<sub>1c</sub> difference between entry and follow-up ( $P = 0.039$ ) were associated with deterioration of renal function (Table 6). The nonsignificant  $P$  value of the likelihood ratio test ( $P = 0.5876$ ) showed an adequate goodness-of-fit for the model used (14). Smoking was the most important factor. No other variables (e.g., BP or protein intake) showed significant effects when entered into the final model including pack years, 24-h sodium excretion, and HbA<sub>1c</sub>. Finally, supine, standing, and sitting BP values were entered into a logistic multiple regression model that did not

Table 2—BP values at baseline and at follow-up

	Nonsmokers		Ex-smokers		Smokers	
	Baseline	Follow-up	Baseline	Follow-up	Baseline	Follow-up
n	35		24		34	
BP (mmHg)						
Supine						
sBP	146 ± 18	145 ± 20	154 ± 14	152 ± 27	151 ± 17	149 ± 19
dBP	86 ± 13	85 ± 12	91 ± 10	88 ± 17	88 ± 12	85 ± 9
Standing after 1 min						
sBP	135 ± 21	125 ± 18	142 ± 19	133 ± 18	137 ± 21	131 ± 20
dBP	88 ± 12	84 ± 11	90 ± 13	86 ± 12	89 ± 12	84 ± 11
Standing after 3 min						
sBP	130 ± 17	127 ± 17	141 ± 21	134 ± 18	137 ± 22	132 ± 17
dBP	87 ± 11	84 ± 12	90 ± 13	86 ± 13	88 ± 11	83 ± 9
Sitting						
sBP	140 ± 18	137 ± 16	149 ± 15	148 ± 22	148 ± 21	143 ± 18
dBP	86 ± 12	85 ± 10	90 ± 11	87 ± 12	88 ± 14	84 ± 10

Data are means ± SD.

Table 3—Proteinuria, creatinine clearance, serum creatinine, and progression rate according to stage of nephropathy

	Nonsmokers nephropathy		Ex-smokers nephropathy		Smokers nephropathy	
	Incipient	Overt	Incipient	Overt	Incipient	Overt
n	20	15	9	15	8	26
Proteinuria (mg/24 h)						
At baseline	178 ± 175	2538 ± 2327	150 ± 202	4445 ± 3712	276 ± 235	3290 ± 3283
At follow-up	190 ± 234	1592 ± 1694	196 ± 179	5423 ± 6031	441 ± 450	2547 ± 2011
Serum creatinine (μM)						
At baseline	88 ± 9	124 ± 35	88 ± 9	150 ± 53	97 ± 18	141 ± 53
At follow-up	88 ± 18	124 ± 35	97 ± 9	186 ± 106	88 ± 18*	150 ± 70
Creatinine clearance (ml · s <sup>-1</sup> · 1.73m <sup>-2</sup> )						
At baseline	1.56 ± 0.39	1.29 ± 0.75	1.72 ± 0.66	1.19 ± 0.48	1.67 ± 0.31	1.21 ± 0.53
At follow-up	1.60 ± 0.46	1.22 ± 0.26	1.46 ± 0.26	1.14 ± 0.60	1.99 ± 0.99	0.99 ± 0.60†
Patients with progression of nephropathy n (%)	1 (5)‡	3 (20)§	2 (22)	6 (48)	4 (50)‡	14 (54)§

Data are means ± SD.

\*P = 0.049 compared with respective baseline values (Student's *t* test for dependent samples).

†P = 0.025 compared with respective baseline values (Student's *t* test for dependent samples).

‡P = 0.015 between nonsmokers and smokers with incipient nephropathy (one-tailed Fisher's exact test).

§P = 0.039 between nonsmokers and smokers with overt nephropathy (one-tailed Fisher's exact test).

include sodium excretion. Again, neither supine, standing, or sitting sBP or dBp values nor the difference between respective baseline and follow-up values were predictive of the progression of nephropathy. ORs for progression of diabetic nephropathy were 2.74 if cigarette pack years increased by 10, 1.70 if sodium excretion increased by 50 mmol/24 h, and 1.65 if HbA<sub>1c</sub> difference increased by 1% (Table 6).

**CONCLUSIONS**— In diabetic patients, mortality rates increase excessively with the onset and progression of diabetic nephropathy (17). In a retrospective investigation, total consumption

of tobacco was reported to increase the risk of end-stage renal failure and death in diabetic patients (18). In this study, smoking was found to be the most important risk indicator for progression of both incipient and overt diabetic nephropathy in hypertensive-treated type I diabetic patients. In a previous cross-sectional investigation, we have found smoking to be more prevalent in patients with overt diabetic nephropathy but not in those with incipient diabetic nephropathy (7). These findings suggest that smoking could be a risk factor for progression rather than incidence of diabetic nephropathy. This is confirmed by the present prospective follow-up results

and may serve to explain the increased prevalence of patients with overt nephropathy among smokers (7) and, in part, their increased morbidity and mortality (18–21). Smoking increases carboxyhemoglobin concentrations, platelet aggregability, and fibrinogen concentrations, all of which may result in tissue hypoxia and contribute to vascular damage (4). In addition, smoking may acutely raise BP and thereby affect kidney function (22).

In a recent study, smoking and metabolic control were found to be independent risk indicators for the development and progression of borderline to increased albuminuria in normotensive diabetic adolescents and young adults in

Table 4—Nonsmokers, ex-smokers, and smokers with progression of nephropathy according to the various definitions of progression

	n	Proteinuria n (%)	Creatinine clearance n (%)	Serum creatinine n (%)	Creatinine clearance and serum creatinine n
Nonsmokers	4	1 (72)	0	3 (34)	0
Ex-smokers	8	2 (475)	2 (45)	6 (71)	2
Smokers	18	5 (296)	6 (39)	8 (30)	1

Numbers of patients with progression by each definition are higher than the total number of patients with progression in each group because some patients had progression by more than one parameter. (n), Mean percentage of change.

Table 5—Comparison of patients without and with progression of nephropathy

	Patients without progression		Patients with progression	
	Baseline	Follow-up	Baseline	Follow-up
n	63		30	
F/M	32/31		13/17	
Age (years)	36 ± 9		36 ± 8	
Diabetes duration (years)	23 ± 8		21 ± 4	
Cigarette pack years (n)	7.4 ± 10*		16.1 ± 15.6*	
HbA <sub>1c</sub> (%)	7.6 ± 1.4	7.3 ± 1.0†	7.8 ± 1.6	8.1 ± 1.5†
BMI (kg/m <sup>2</sup> )	24 ± 3	24 ± 4	24 ± 2	25 ± 2
Sodium excretion (mmol/24 h)	184 ± 97	170 ± 70†	163 ± 69	210 ± 84†
Protein intake (g/kg body weight)	1.0 ± 0.4	0.9 ± 0.3	0.9 ± 0.3	0.9 ± 0.3
Sitting BP (mmHg)				
sBP	143 ± 17	139 ± 18	148 ± 21	146 ± 21
dBP	87 ± 13	85 ± 10	90 ± 12	85 ± 12

Data are means ± SD.

\*P = 0.001, Wilcoxon's rank-sum test.

†P = 0.026, Wilcoxon's rank-sum test.

‡P = 0.052, Wilcoxon's rank-sum test.

fair metabolic control and with early diabetic late complications (23). This study extends these findings for hypertensive patients with established nephropathy and rather good control of blood glucose and BP values. The influence of metabolic control on the progression of overt diabetic nephropathy remains controversial (2,24,25). In this study, metabolic control was of borderline significance for the progression of nephropathy, whereas the number of pack years was the most

important predictor for the progression of nephropathy.

Because a low socioeconomic status is associated with smoking, we cannot exclude the possibility that social factors could have contributed to our results. However, in a recent follow-up study of patients with lupus nephritis (26), smoking was strongly associated with the development of renal failure independently of the socioeconomic status of the patients.

To date, the effect of sodium intake on the progression of diabetic nephropathy is unknown. Interestingly, in this study, a higher sodium intake, as calculated from 24-h urine sodium excretion, was associated with progression of nephropathy. In chronic glomerulonephritis, salt restriction reduces total peripheral vascular resistance (26). In hypertensive subjects, high salt intake results in enhanced renal vasoconstriction and decreased renal blood flow (28). These changes may have a negative effect on renal function when kidney damage is already present.

In this study, BP values recorded while patients were not smoking were not associated with progression of nephropathy. Note that all of the patients were under intensive antihypertensive therapy. Although clinical BP values were above normal in some patients, according to home monitoring, BP values remained in the normotensive range in almost all patients. This study was not conducted to determine the influence of different levels of BP control on kidney function. However, the total lack of influence of BP values on progression of nephropathy in any statistical model of multiple regression is highly supportive for the lack of a major difference in progression between patients with high or low normal BP values.

In conclusion, smoking represents an important factor associated with progression of diabetic nephropathy in patients who are intensively treated for hypertension. In addition, metabolic control and sodium intake seem to play a role in this context. Studies dealing with progression of diabetic nephropathy should be controlled for smoking habits.

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Table 6—Results of logistic regression analysis

	Cigarette pack years	Sodium excretion	HbA <sub>1c</sub> difference
Regression coefficient	0.1008	0.016	0.5018
SE	0.0285	0.0043	0.2432
Standardized estimate	0.7131	0.4467	0.3583
Wald $\chi^2$ test	12.54	6.26	4.26
P value	0.0004	0.0123	0.0391
Difference for OR	10 pack years	50 mmol/24 h	1%
OR	2.74	1.70	1.65
95% CI	1.57–4.81	1.11–2.56	1.03–2.66

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