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Rapid communication

Cigarette-smoking as a risk factor for macroproteinuria and proliferative retinopathy in Type 1 (insulin-dependent) diabetes

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Summary. In a case control study 192 cigarette-smoking patients with Type 1 (insulin-dependent) diabetes were compared with 192 non-cigarette-smoking patients pair-matched for sex (90 females), duration of diabetes (mean 14 years), and age (mean 32 years). Macroproteinuria was found in 19.3% of the smoking and in 8.3% of the non-smoking patients ($p < 0.001$). Proliferative retinopathy was present in 12.5% of the smoking and in 6.8% of the non-smoking patients ($p < 0.025$). The percentages of patients with normal proteinuria or without retinopathy were comparable between the two groups. In addition, glycosylated haemoglobin values and the prevalence of hypertension were similar between smoking and non-smoking patients. Thus, cigarette-smoking appears to be a risk factor for the progression of incipient to overt nephropathy and of background to proliferative retinopathy in Type 1 diabetes.

Key words: Diabetes, smoking, diabetic nephropathy, diabetic retinopathy.

In a number of recent reports on the influence of blood pressure [1] or metabolic control [2-3] on the course of diabetic nephropathy or retinopathy, cigarette-smoking has not been mentioned as a criterion for patient selection or as a possible confounding factor for the outcome of the studies. Thus, it appears to be accepted that smoking does not present a risk factor for the development or progression of diabetic microangiopathy. In fact, studies on this topic are scarce, although a few investigations have suggested an association between cigarette-smoking and advanced states of diabetic renal and eye disease [4-6].

In the present study we provide evidence that cigarette-smoking is associated with macroproteinuria and proliferative retinopathy in Type 1 (insulin-dependent) diabetic patients.

Subjects and methods

Between 1981 and 1985, 1254 adult Type 1 diabetic patients (651 women, 603 men; age 30 ± 13 years; duration of diabetes 10 ± 8 years; mean ± SD) participated in our 5-day inpatient diabetes treatment and teaching programme [7]. Patients with endstage renal failure are usually not referred to this programme. Twenty-five percent of the female and 39% of the male patients reported to be currently cigarette-smokers.

Out of this cohort 90 female and 102 male cigarette-smoking patients with a duration of diabetes of at least 6 years could be pair-matched with non-smoking patients with respect to sex, duration of diabetes (± 1 year) and age (± 2 years). Patients with urinary tract infections were not considered eligible for this study. Age and duration of diabetes of the smoking and non-smoking patient groups are shown in Table 1. In the smoking patient group 55 female and 45 male patients smoked less than 20 cigarettes per day, 31 female and 50 male patients smoked between 20 and 39, and 4 female and 7 male patients smoked 40 or more cigarettes per day. Nineteen smoking and 17 non-smoking patients used oral contraceptives, and 2 smoking and 4 non-smoking women were pregnant.

During the hospital stay each patient collected a 24-h urine sample for determination of proteinuria and creatinine clearance. Proteinuria was measured with a laser-turbidimeter (Lasermed GmbH, Cologne, FRG) as described recently [8]. Using this method, the minimal detectable urine protein concentration was 15 mg/l; the intraassay coefficient of variation was 2.7% and the interassay coefficient of variation 5.8%. The upper normal range (mean + 2SD), based upon 50 healthy individuals, was 60 mg protein per 24 h. Values between 60 and 500 mg per 24 h were considered microproteinuric, and of 500 mg or more as macroproteinuric. Glycosylated haemoglobin values were measured by the thiobarbiturate method (normal range 4.2-5.6%, mean ± 2SD). Serum triglyceride, cholesterol, HDL-cholesterol and creatinine levels were determined by routine laboratory methods. Body mass index (kg/m^2), daily insulin dosage (U/kg per day) and antihypertensive medication were recorded. Blood pressure was measured according to WHO criteria 5 to 15 times per patient, and the mean of all readings was included in the analyses. Retinopathy was assessed by a consultant ophthalmologist by direct ophthalmoscopy with the pupils dilated and graded as nil, background or proliferative retinopathy. Data are given as mean ± SD. The chi-square test was used for statistical analysis.

Results

There were no significant differences between the smoking and the non-smoking patient group with respect to body mass index (22.5 ± 2.5 versus 23.1 ± 3.0

Table 1. Clinical data, metabolic control and prevalence of proteinuria, retinopathy and hypertension in smoking and non-smoking Type 1 diabetic patients

	n	Age (years)	Duration of diabetes (years)	HbA_{1c} (%)	Patients with normal proteinuria	Patients with macro-proteinuria	Patients without retinopathy	Patients with proliferative retinopathy	Patients with hypertension[d]
Smokers									
Females	90	30±11	14±6	7.9±1.6	53.3%	14.4%[a]	63.3%	13.3%[b]	11.1 (20.0)%
Males	102	34±12	14±6	8.4±2.2	44.1%	23.5%[b]	53.9%	11.8%	14.7 (38.2)%
Total	192	32±11	14±6	8.2±1.9	48.4%	19.3%[c]	58.3%	12.5%[a]	13.0 (29.7)%
Non-smokers									
Females	90	30±11	14±6	8.3±2.2	64.4%	5.6%	60.8%	3.3%	7.8 (22.2)%
Males	102	33±11	14±6	7.9±1.7	50.0%	10.8%	57.8%	9.8%	15.7 (34.3)%
Total	192	32±11	14±6	8.1±2.0	56.8%	8.3%	59.4%	6.8%	12.0 (28.6)%

[a] $p<0.025$, [b] $p<0.01$, [c] $p<0.001$ compared to non-smoking reference group; [d] blood pressure values ≥160/95 mmHg or antihypertensive medication, in parentheses blood pressure values ≥140/90 mmHg or antihypertensive medication

kg/m^2), daily insulin dosage (0.72±0.22 versus 0.70±0.23 U/kg per day), glycosylated haemoglobin values (Table 1), serum triglyceride (1.8±1.1 versus 1.5±1.0 mmol/l), cholesterol (5.8±1.5 versus 5.4±1.3 mmol/l) and HDL cholesterol values (1.3±0.5 versus 1.3±0.4 mmol/l), serum creatinine levels (104±40 versus 102±60 μmol/l), and the percentage of patients with hypertension (Table 1). In addition, the percentages of patients with normal proteinuria levels or without retinopathy were not significantly different between the smoking and non-smoking patients (Table 1). However, the percentages of patients with macroproteinuria or proliferative retinopathy were significantly higher in the smokers than in the non-smokers (Table 1); the difference with respect to proliferative retinopathy was significant only for women and for the total group. Patients with macroproteinuria also had in a high percentage proliferative retinopathy, hypertension, a creatinine clearance below 80 ml/min and serum creatinine levels above 130 μmol/l, but the prevalence of these complications was not different between macroproteinuric smoking and non-smoking patients.

Discussion

These data demonstrate that, after an average duration of diabetes of 14 years, macroproteinuria and proliferative retinopathy were twice as frequent in Type 1 diabetic patients who were cigarette-smokers as in non-cigarette-smoking patients. Since the percentages of patients with normal proteinuria or without retinopathy were comparable between smoking and non-smoking patients, the study suggests that smoking represents a risk factor for the progression of incipient to overt nephropathy and from background to proliferative retinopathy.

This investigation is not the first report claiming an association between smoking and advanced diabetic late complications. In 1977 Paetkau et al. [4] postulated that smoking might contribute to the progression of diabetic retinopathy from the simple background state to the proliferative state. Subsequently Christiansen [5] found a significantly higher prevalence of nephropathy (macroproteinuria) in smoking than in non-smoking insulin-dependent juvenile-onset diabetic patients, although background retinopathy and proliferative retinopathy were no more common than in the non-smoking patients. An association between advanced renal disease and smoking has also been observed by other authors [6]. On the other hand, these studies have been criticized [5, 9] because of small patient numbers, heterogeneity of patients with respect to type of diabetes and duration of disease, and lack of assessment of metabolic control. In addition, in a recent case control study [10] comparing Type 1 diabetic patients with no or only minimal retinopathy and patients with proliferative retinopathy, smoking did not evolve as a risk factor. However, this recent study [10] and the findings of Paetkau et al. [4] are well in accordance with the results of the present investigation. They support the assumption that smoking does not initiate abnormal retinal vessels, but might exert a devastating influence only after non-proliferative retinopathy has manifested itself. They lend support to the view that non-proliferative retinopathy evolves due to hyperglycaemia, whereas the progression to proliferative retinopathy is dependent on various factors inducing retinal neovascularization [10]. Smoking increases carboxyhaemoglobin levels; this hampered oxygen delivery to a hypoxic sensory retina may exert retinal neovascularization. Similar pathophysiological mechanisms might be operative for the progression from incipient to overt diabetic nephropathy.

In contrast to these previous studies [4–6, 10], the present investigation was performed in order to particularly investigate the role of smoking by comparing matched pairs of Type 1 diabetic patients with identical sex, duration of diabetes and age. In addition, the two patient groups presented with a comparable status of other established risk factors for the initiation or progression of diabetic microangiopathy, such as glycosylated haemoglobin, blood pressure or serum triglyceride

levels. Thus, through this particular study design it was possible to evaluate the independent contribution of smoking on diabetic renal and eye disease.

In this study, recent changes in the patients' smoking status were not recorded, as only present smoking habits were included in the analyses. If ex-smokers would have been excluded from the non-smoking patient groups, one would have expected, as suggested by Christiansen [5], that the documented association between smoking and advanced diabetic microvascular disease had, if anything, been even closer.

In conclusion, we have shown that cigarette-smoking is closely associated with the prevalence of macroproteinuric nephropathy and proliferative retinopathy in Type 1 diabetic patients, independent of hitherto established risk factors for the development of diabetic microvascular disease. Thus, we suggest that smoking status needs be taken into account in future prospective studies on the course of diabetic late complications.

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