SMOKING HABIT AND PROGRESSION OF DIABETIC NEPHROPATHY

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Abstract: The effect of cigarette smoking on the progression of diabetic nephropathy was evaluated cross-sectionally in 155 patients with non-insulin-dependent diabetes mellitus of at least 5 years duration. Forty-four patients had a smoking habit. There was no difference in the duration of diabetes, mean value of HbA_1c, or the prevalence of hypertension between the smokers and nonsmokers. However, there was a significant difference in the distribution of a smoking habit among subgroups of diabetic patients with normoalbuminuria, microalbuminuria, and overt proteinuria. Thus, cigarette smoking in patients with diabetes is concluded to be a risk factor for the development of diabetic nephropathy.

Index Terms

diabetic nephropathy, microalbuminuria, non-insulin-dependent diabetes mellitus, smoking

INTRODUCTION

The adverse effects of smoking on general health are well known. It was recently reported that the kidney is an important target organ for damage caused by smoking[1]. Evidence shows that cigarette smoking is associated with the development of diabetic nephropathy[2-14]. Such data have been collected mainly in patients with insulin-dependent diabetes mellitus (IDDM), rather than in those with non-insulin-dependent diabetes mellitus (NIDDM). There is little information on the effects of cigarette smoking on diabetic nephropathy in Japanese subjects. The present study investigated the possible relationship between cigarette smoking and the risk of diabetic nephropathy in Japanese patients with NIDDM.

SUBJECTS and METHODS

The study group was comprised of 155 Japanese patients with NIDDM (72 males and 83 females) with a disease duration of at least 5 years. Patients were divided into three groups based on the urinary excretion of albumin: normoalbuminuria (NA, $<20\ \mu g/min$), microalbuminuria (MA, 20-200 $\mu g/min$), and overt proteinuria (OP, $>200\ \mu g/min$). Their smoking habit was recorded at clinic visit. A smoker was defined as one who had smoked five or more cigarettes per day for 1 year or longer. Information was also collected on the duration of diabetes, the level of glycosylated hemoglobin (HbA_1c), the presence of hypertension and diabetic retinopathy, and treatment modality.

Statistical analysis

Data are presented as mean±SD. An unpaired t-test was used in evaluating mean differ-

ences, and chi-square test was used for comparisons. A level of $p<0.05$ was considered statistically significant.

RESULTS

The patients' clinical characteristics are shown in Table 1. Except for mean age (66.5±8.9 vs. 63.2±9.7 years), there were no significant differences between the nonsmokers and smokers with respect to duration of diabetes, BMI, HbA_1c, the percentage of those with hypertension and diabetic retinopathy, and treatment modality. There was a significant difference in the distribution of smoking habit among the patients with normoalbuminuria, microalbuminuria and overt proteinuria ($\chi^2=6.17$, $p<0.05$) (Table 2).

DISCUSSION

Several authors have suggested possible links between smoking and diabetic nephropathy[2,4-11,13,14] (Table 3). Christiansen[2] in 1978 suggested that smoking is an independent risk factor for diabetic nephropathy. Several studies showed that the risk of developing microalbuminuria or proteinuria is substantially higher in people who smoke. Chase et al.[8] reported that the prevalence of abnormal albumin excretion was 2.8-fold higher in smokers than nonsmokers. Telmer et al.[4] also reported that the prevalence of overt proteinuria was 1.6-fold higher in smokers than nonsmokers. Klein et al.[9] reported in the Wisconsin Study that the relative risk of progressing from microalbuminuria to overt proteinuria in a 4-year period was 2.0- to 2.5-fold higher in smokers vs nonsmokers. In the prospective investigation by Sawichi et al.[10], in which possible factors associated with the progression of diabetic nephropathy over a one-year period were evaluated in 92 patients with IDDM, a progression of nephropathy was found in 53 % of the smokers as compared with 11 % of the nonsmokers, even though all patients were receiving insulin and antihypertensive therapy. Our results agree with those of previous reports.

In contrast, West et al.[3] reported a lack of association between smoking and proteinuria.

Table 1. Patient characteristics

Item	Nonsmokers	Smokers
Number	111	44
Sex (M/F)	35/76	37/7
Age (yr)	66.5±8.9	63.2±9.7*
Duration of diabetes (yr)	13.9±7.9	13.1±6.9
BMI (kg/m^2)	23.1±3.2	22.6±2.8
HbA_1c (%)	7.2±1.3	7.4±1.4
Hypertension (%)	56	50
Retinopathy (%)	44	56
Treatment		
Diet	20	8
OHA	58	20
Insulin	33	16

BMI, body mass index; OHA, oral hypoglycemic agent.
*$p<0.05$ vs nonsmokers

Table 2. Distribution of stage of diabetic nephropathy in nonsmokers and smokers

Stage of diabetic nephropathy	Nonsmokers	Smokers
Normoalbuminuria	61 (55%)	16 (36%)
Microalbuminuria	34 (31)	15 (34)
Overt proteinuria	16 (14)	13 (30)

Data are n (%)

Table 3. Review of literature concerning influence of smoking on the progression of diabetic nephropathy

Author	Country	Study design	Diagnosis	Number of patients	Adverse effect of smoking
Christiansen (1978)	Denmark	Cross-sectional	IDDM	180	OP
West (1980)	USA	Cross-sectional	NIDDM †	973	no association
Telmer (1984)	Denmark	Cross-sectional	IDDM	668	OP
Norden (1984)	Sweden	Cross-sectional	IDDM	94	OP, decreased GFR
Muhlhauser (1986)	Germany	Case-control	IDDM	384	OP
Stegmayer (1990)	Sweden	Retrospective analysis	IDDM	34	Life-threatening ESRD
Chase (1991)	USA	Cross-sectional	IDDM	359	MA
Klein (1993)	USA	Follow-up	NIDDM	839	OP
Sawicki (1994)	Germany	Follow-up	IDDM	93	OP, increased Scr
Couper (1994)	Australia	Cross-sectional	IDDM	169	MA
Lee (1994)	USA	Follow-up	NIDDM †	912	no association
Bruno (1996)	Italy	Cross-sectional	NIDDM	1571	MA, OP
Biesenbach (1997)	Austria	Follow-up	NIDDM	37	decreased GFR
Present study	Japan	Cross-sectional	NIDDM	155	MA, OP

MA, microalbuminuria ; OP, overt proteinuria ; ESRD, end-stage renal disease ;
Scr, serum creatinine ; GFR, glomerular filtration rate.
† ; Oklahoma Indians

Those authors showed that the incidence of proteinuria was similar in smokers and nonsmokers among Oklahoma Indians with adult-onset diabetes. Lee et al.[12] also reported that cigarette smoking was not a statistically significant predictor of renal failure among Oklahoma Indians with adult-onset diabetes. However, the failure to find such an association may be related to the selected population studied. Although these results remain to be substantiated, it appears that smoking is a risk factor for diabetic nephropathy.

The mechanism by which tobacco consumption enhances microvascular damage has not yet been fully clarified. Smoking (or nicotine) increases the carboxyhemoglobin concentration, platelet aggregability, and fibrinogen concentration, all of which may cause tissue hypoxia and contribute to vascular damage[1,15]. Smoking may inhibit prostacyclin formation, as well as elevate the blood pressure[1,16,17]. Smoking (or nicotine) is reported to have three major effects on the kidney[1] : 1) Nicotine increases the glomerular filtration rate which is mediated by the release of catecholamines from the adrenals. Ekberg et al.[18] reported that the prevalence of hyperfiltration in smokers was 41 % as compared with 18 % in nonsmokers. The increase in the glomerular filtration rate induced by smoking may be involved in the development of hyperfiltration as a mediator of the progression of diabetic nephropathy. 2) Smoking is associated with a suppression of water excretion. Nicotine reportedly exerts an antidiuretic effect, probably due to an increase in vasopressin secretion[19]. Antidiuresis is therefore a potential factor in the progression from diabetic nephropathy to chronic renal failure. 3) Smoking has a direct effect on proximal tubular damage. An increase in the urinary excretion of N-acetyl-beta-glucosaminidase has been correlated with the number of cigarettes smoked[20]. Other adverse effects of smoking on diabetes include the development of insulin resistance and of endothelial cell dysfunction. Facchini et al.[21] reported that smokers show a decrease in insulin sensitivity, while Eliasson et al.[22] reported that smoking is correlated with the degree of insulin resistance. Endothelial cell-dependent vasodilation is impaired in smokers as

compared with nonsmokers. Such vasodilation in also implicated in the pathogenesis of glomerular injury.

The results of the present study strongly suggest the importance of educating or advising the patient with diabetes to give up smoking. Although it remains to be determined whether the cessation of smoking can halt the progression of diabetic nephropathy, a modification of the lifestyle including giving up smoking must be heeded by all patients with diabetes.

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