Smoking as a Risk Factor for Nephropathy in Non-Insulin-Dependent Diabetics

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This study examines whether there was an association between smoking and nephropathy in patients with non-insulin-dependent diabetes mellitus enrolled in the Appropriate Blood Pressure Control in Diabetes Trial. Sixty-one percent of the patients were smokers; 26% had microalbuminuria, and 14% had overt nephropathy. There was a univariate association between diabetic nephropathy and gender, smoking status, duration of diabetes, hypertension, glycosylated hemoglobin level, creatinine level, body mass index, and cholesterol level. Stepwise logistic regression demonstrated an independent association between smoking and diabetic nephropathy (odds ratio 1.61; 95% confidence interval 1.01, 2.58). These findings may have important implications for patients with non-insulin-dependent diabetes mellitus who smoke.

KEY WORDS: nephropathy; non-insulin-dependent diabetes mellitus; smoking.

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Non-insulin-dependent diabetes mellitus (NIDDM) has increased in prevalence 700% over the last 40 years.¹ Most of its economic impact emanates from the treatment of NIDDM complications. One of these complications, diabetic nephropathy, is a leading cause of end-stage renal disease.² Microalbuminuria, defined as an albumin excretion rate of 30 to 300 mg per day, is the first clinical sign of diabetic nephropathy.³ The main approaches to the prevention of renal disease in NIDDM have been the treatment of hyperglycemia and treatment of hypertension⁴; smoking cessation has not been promoted as a means to reduce nephropathy in patients with NIDDM.⁵ Part of this neglect may be explained by the lack of a clear association between nephropathy and smoking.³ Therefore, we examined the relation between smoking and nephropathy in patients with NIDDM, using baseline data from the Appropriate Blood Pressure Control in Diabetes (ABCD) trial.

METHODS

Study Population

The ABCD Trial was a prospective, randomized trial of NIDDM patients designed primarily to determine the ef-

fects of different intensities of blood pressure control on diabetic complications.^{6,7} Study participants were between the ages of 40 and 74 years with a diastolic blood pressure of 80 mm Hg or higher. The patients were identified from the pharmacy lists of health care systems in the Denver area. Enrolled subjects were receiving no antihypertensive medications at the time of randomization. Patients were excluded if they had a history of a myocardial infarction, unstable angina, New York Heart Association class IV heart failure, an absolute need for angiotensin-converting enzyme (ACE) inhibitors or calcium-channel blockers, or a serum creatinine level greater than 3mg/dL (265 μ mol/L). Institutional Review Board approval was obtained for the conduct of this trial.

Procedures

Assessment of Blood Pressure. Blood pressure measurements were taken after cessation of preexisting antihypertensive medications. The mean of three measurements was used for analysis.

Urinary Albumin Excretion. Urinary albumin excretion (UAE) was measured on three occasions. Microalbuminuria of 30 to 300 mg per day was classified as no nephropathy, while diabetic nephropathy was defined as more than 300 mg of urinary albumin in a 24-hour period. During the first part of the study, UAE was measured by the nephelometric method, and thereafter UAE was measured using radioimmunoassay (Double Antibody Albumin Diagnostics, Los Angeles, Calif.). The correlation coefficient between results from the two methods was $r^2 = .99$ ($n = 68$).

Definitions

Patients were categorized by cigarette smoking status as former, current, or nonsmokers. Subjects were considered to be nonsmokers if they had smoked fewer than 100 cigarettes in their lifetime (pack years = 0); former smokers if they had smoked more than 100 cigarettes but had stopped smoking; and current smokers if they had smoked more than 100 cigarettes and continued to smoke. The number of pack years as well as the duration of diabetes and hypertension were defined by self-report.

Statistics

The Statistical Analysis Software (SAS) system was used for all analyses. When the baseline characteristic was continuous, for example, age, duration of diabetes, blood pressure, serum creatinine level, body mass index (BMI), and pack years, a two-sample Student's *t* test was

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performed. We used χ^2 analyses when the baseline characteristics were categorical, for example, gender, smoking status, and race/ethnicity. Multiple logistic regression was used when evaluating the effects of covariates on nephropathy. Odds ratios (ORs) and the corresponding confidence intervals (CIs) were calculated from logistic regression estimates. When the outcome variable was non-normally distributed, nonparametric analyses or parametric analyses on suitably transformed variables were performed. All values are reported as a mean $\pm$ SD.

RESULTS

Baseline Characteristics

The baseline characteristics for the ABCD Trial population are shown in Table 1: 61% were either current or former smokers, the average age was 58.2 ± 8.3 SD years, and 61% of the patients were male. The number of pack years smoked was similar for current and former smokers, and there was no difference in nephropathy between current and former smokers when they were compared with nonsmokers in a multivariate model. Thus, current and former smokers were combined into a new category called "smoker." Baseline characteristics of the smokers and nonsmokers were similar except that there were more male smokers. Normoalbuminuria was found in 60% of the patients; 26% had microalbuminuria, while 14% had nephropathy.

Diabetic Nephropathy

Initially, we performed univariate analyses for patients with and patients without diabetic nephropathy ($n = 949$). These analyses demonstrated an association between diabetic nephropathy and gender, smoking status (OR 1.51; 95% CI 1.02, 2.23), duration of diabetes and hypertension, blood pressure, glycosolated hemoglobin level, creatinine level, BMI, and cholesterol level.

Results of fitting the stepwise logistic regression model for diabetic nephropathy are presented in Table 2 ($n = 903$). Variables that were independently associated with diabetic nephropathy included smoking status, race/ethnicity, duration of diabetes, serum creatinine level, uric acid, blood pressure, glycosolated hemoglobin level, triglycerides, and age. Of note is the independent association of smoking status with diabetic nephropathy (OR 1.61; 95% CI 1.01, 2.58).

For the multivariate logistic model, 46 (4.8%) of the 950 subjects were dropped because they had missing data for at least one of the variables considered for entry into the model. The unadjusted OR of 1.43 for smoking status in this reduced sample size (95% CI 0.96, 2.13) compares favorably with that for the full sample. Furthermore, adjustment for potential confounders individually, or together, produced only small changes in the OR for smoking status.

Table 1. Baseline Characteristics of the Appropriate Blood Pressure Control in Diabetes Trial Population*

Variable	n	Values
Gender, %	950	
Male	579	60.9
Female	371	39.1
Age, years $\pm$ SD	950	58.2 ± 8.3
Smoking status, %	950	
Current		13.5
Former		47.2
Nonsmoker		39.4
Pack years of smoking	947	19.7 ± 29.2
Duration of diabetes, years $\pm$ SD	950	8.8 ± 6.9
Duration of hypertension, years $\pm$ SD	950	9.4 ± 10.1
SBP at randomization, mm Hg $\pm$ SD	949	146.0 ± 19.0
DBP at randomization, mm Hg $\pm$ SD	950	91.1 ± 8.5
Race, %	950	
Non-Hispanic white		70.6
African American		11.9
Hispanic		15.2
Other		2.3
Glycosolated hemoglobin, % $\pm$ SD	931	11.6 ± 3.2
Body mass index, kg/m ² $\pm$ SD	948	31.5 ± 5.9
Albuminuria status, %	949	
Normal (<30 mg/d)		60.0
Micro (30–300 mg/d)		25.9
Overt (>300 mg/d)		14.1
Insulin treatment, %	950	42.9
Oral agents, %	950	56.9
PVD, %	928	12.5
Coronary artery disease, %	950	23.2
ACE inhibitor, %	950	28.7

*SBP indicates systolic blood pressure; DBP, diastolic blood pressure; PVD, peripheral vascular disease; ACE, angiotension-converting enzyme.

It is also of interest to investigate the ORs when smoking status is classified into three levels (current, past, and never) rather than two levels (ever smoke and never). The univariate ORs for current and former smokers as compared with nonsmokers were 1.29 and 1.57, respectively. However, the multivariate ORs for current and former smokers as compared with nonsmokers were 1.60 and 1.62, respectively. These multivariate ORs are very similar to each other and to the multivariate OR when former and current smokers were combined into one group.

DISCUSSION

Diabetes is a leading cause of nephropathy. Smoking has been found to be associated with diabetic nephropathy in patients with insulin-dependent diabetes mellitus.^{8,9} In nondiabetic patients, there are also data to suggest that smoking is a risk factor for nephropathy.¹⁰

In contrast, the role of smoking in the pathogenesis of nephropathy in NIDDM has been uncertain. Smaller

Table 2. Logistic Regression Model for Nephropathy

Variable	Odds Ratio	95% Confidence Interval	p Value	Change for Continuous Variables
Smoking status	1.614	1.008, 2.584	.0463	
Race/Ethnicity				
Hispanic vs	4.629	2.642, 8.111	.0001	
African American vs	2.203	1.205, 4.029	.0103	
Duration of diabetes	1.855	1.363, 2.524	.0001	10 years
Serum creatinine	4.869	2.012, 11.785	.0004	1 mg/dL
Uric acid	1.459	1.238, 1.720	.0001	1 mg/dL
Systolic blood pressure	1.455	1.287, 1.645	.0001	10 mm Hg
Glycosolated hemoglobin	1.359	1.131, 1.633	.0011	2.5%
Triglyceride	1.030	1.002, 1.058	.0326	50 mg/dL
High density lipoprotein	0.881	0.791, 0.981	.0215	5 mg/dL
Age	0.846	0.729, 0.982	.0278	5 years

studies have not demonstrated a significant association in NIDDM.¹¹⁻¹³ In the present study, a significant association was demonstrated between smoking and the risk of nephropathy. This relative risk (OR 1.61) of smoking for nephropathy in NIDDM is comparable to its relative risk for coronary heart disease (OR 1.54; 95% CI 1.49, 1.58) and peripheral vascular disease (OR 1.99; 95% CI 1.23, 3.22).¹⁴ Smoking has not consistently been found to be an important risk factor for retinopathy or neuropathy in NIDDM.

The exact mechanism whereby smoking might cause nephropathy is nebulous. Theories have proposed that increased tissue hypoxia from carboxyhemoglobin causes an increased production of potent, and a decreased production of vasodilatory prostacyclins.¹⁵

A potential limitation of this study is its cross-sectional design, which precludes the demonstration of a causal relation between smoking and nephropathy in NIDDM. The relation we have demonstrated, however, indicates interventional studies are needed to evaluate whether smoking cessation will attenuate the risk of nephropathy.

A second limitation is that we relied on a self-reported history for smoking status and the duration of diabetes. However, there is little reason to believe that patients with nephropathy would be more likely to misclassify this information.

A third limitation is that former smokers could have stopped smoking for reasons related to nephropathy or a precursor of nephropathy. Thus, by combining the current and former smokers, we could be masking important information pertaining to these two groups. However, we feel that the probability of this bias is minimal because the multivariate ORs were similar for current and former smokers.

Despite these potential limitations, we have demonstrated a clear association between smoking and nephropathy in NIDDM. Currently, in the United States 27% of diabetics report smoking cigarettes.⁵ Finding another potential hazard of smoking in patients with diabetes gives

physicians further evidence to utilize when encouraging smoking cessation.^{16,17}

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REFLECTIONS

The Survivor's Exit

She leans over to the Passenger's side and
wraps the seat belt around the Empty Space.
Click!

"Sit tight," she says.
"Everything's okay," she says.
"We're finally going home."

Fingers wrapped
'round the steering wheel,
she follows blurry
exit signs.
Catches that
familiar red word
a different way
in the rearview mirror:
LATIPSOH.

Tires perched at
the edge
of the driveway.
Soothed for
a moment
by the hum
of the engine
and the tick tick tick
of the turn signal.
Looks left and then right,
left and right,
left, right.
Raises her
lead brow,
forces her
tired shoe
to the pedal.
Says in
her head
everything's okay,
here we go.

And this is
the way
she
must
go.

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