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C O N T E N T S

Cigarette smoking: An environmental risk factor for progression of nephropathy in diabetes

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OBJECTIVE: Diabetic nephropathy is the leading cause of death in diabetics in Pakistan. Various environmental factors are involved in the pathophysiology of the complications of diabetes. Cigarette smoking is foremost among the environmental factors that contributes to the progression of diabetic nephropathy; however, sufficient data on the effect of smoking on the decline in kidney function in diabetic nephropathy are lacking. We assessed the impact of smoking on the progression of diabetic nephropathy in patients with type 1 diabetes. **METHODOLOGY:** A total of 120 diabetic patients with nephropathy (aged between 25 and 75 years) admitted in the diabetic wards of Jinnah Postgraduate Medical Center (JPMC) and Civil Hospital Karachi (CHK), Karachi, were selected for the present study after informed consent was obtained. They were divided into two groups: smokers and non-smokers. Fifty age-matched normal individuals with no known history of smoking, hyperglycemia, and/or renal insufficiency were selected as control. Their height (in meters) and weight (in kilograms) were recorded for calculation of body mass index. Their blood pressures were measured using a standard mercury sphygmomanometer. Fasting blood samples were collected and analyzed for blood glucose, serum sialic acid, urea and creatinine; serum cholesterol, triglyceride, LDL-cholesterol and HDL-cholesterol were measured by spectrophotometric techniques. Glomerular filtration rate (GFR) was calculated. HbA_{1c} was measured by fast ion-exchange resin separation method. **RESULTS:** Compared with non-smokers, smokers had significantly higher values of blood pressure, blood glucose, HbA_{1c}, serum sialic acid, urea, creatinine, cholesterol, LDL-cholesterol and triglyceride. GFR and HDL-cholesterol values were lower in smokers than in nonsmokers. More obese (on the basis of BMI) patients were found among the smokers as compared to nonsmokers. **CONCLUSION:** Smoking is strongly associated with hyperglycemia, dyslipidemia, and decline in GFR, leading to progression of end-stage renal disease in diabetes. Further long-term studies are required to clarify the exact mechanism by which smoking causes decline in renal function.

KEY WORDS: Cigarette smoking, diabetes, nephropathy, risk factor

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Introduction

Approximately 500,000 deaths occur each year from smoking-related causes, making cigarette smoking the leading avoidable cause of death in the United States. The prevalence of smoking among people with diabetes is similar to that in the general population. For smokers with diabetes, however, the complications incurred are much more.[1] All-cause mortality is increased in smokers with diabetes, and the risk of macro and microvascular complications is also increased. Furthermore, smoking has been linked to worsening diabetes control and insulin resistance and may even induce diabetes.[2]

Among Pakistani adults, where 29% of the men are smokers, there is a significantly high prevalence of cardiovascular disease risk factors: 18% suffer from hypertension and 13% have elevated cholesterol levels.[3] The microvascular complications of diabetes, including nephropathy, retinopathy and neuropathy, are strongly linked to metabolic control. Excessively high levels of blood glucose play a central role in triggering the events which subsequently lead to the complications of diabetes. While the association between these and tobacco use have not been studied in detail, it is likely that smoking increases the risk of microvascular complications, especially nephropathy, in people with diabetes.[4] A recent review of smoking and diabetes does not support the evidence that smoking is associated with the development of diabetes.[5] However, previous large prospective studies have suggested that smoking

is associated with the development of diabetes in men and women, with the evidence consistently linking smoking and insulin resistance.[6-8] Recently, the adverse effects of smoking on renal function has drawn attention, mainly through investigations in nondiabetic patients. The adverse effects of smoking on the renal function in diabetic patients, however, have not been investigated extensively. Little is known about the pathophysiological mechanisms involved in the progression of diabetic kidney disease in the presence of smoking. Therefore, the present study aimed to assess the effects of smoking on the progression of renal insufficiency in diabetic patients by means of evaluation of important risk factors and biochemical indicators of diabetic nephropathy.

Methodology

A total of 120 diabetic patients with nephropathy, admitted in the diabetic wards of JPMC and CHK, Karachi, were selected according to the WHO criteria[9] for the present study after informed consent was obtained. Their ages ranged from 25 to 75 years. They were divided into two groups according to their smoking habits: smokers and nonsmokers. A person smoking more than one cigarette a day was considered as a smoker. Fifty age-matched normal individuals with no known history of smoking, hyperglycemia, and renal insufficiency were selected as control. Patients suffering from gestational diabetes, any known mental illness, macrovascular disease prior to diagnosis of type 2 diabetes, or patients who refused to participate in the study were excluded.

A structured questionnaire was used to record the demographic features of all subjects. Height and weight were noted for calculation of the BMI [BMI = weight in kilograms/(height in meters)^2]. BMI ≥30.0 was considered as obese and 20.0-29.9 was considered nonobese overweight. Blood pressure was measured with a standard mercury sphygmomanometer while the patient was sitting after resting for 10 min. Hypertension was defined as a blood pressure ≥ 140/90 mmHg.[10]

Fasting blood samples were collected in lithium heparin-coated tubes after ensuring that the subject had not taken any medication for the last 12 h or longer. Serum sialic acid was estimated by Ehrlich's method.[11] HbA_{1c} was estimated by fast ion-exchange resin separation method (Human Gessellschaft fur Biochemica und Diagnostica mbH, Germany). Fasting blood glucose was measured by the o-toluidine method.[12] Serum urea was estimated by the thiosemicarbazide-diacetyl monoxime method.[13] Serum creatinine was measured by the modified Jaffe's method.[14] Modern and well-established equation methods were used to determine the glomerular filtration rates (GFR).[15] Serum cholesterol, triglyceride, LDL-cholesterol and HDL-cholesterol were measured by spectrophotometric techniques. Data was analyzed using the Statistical Package for Social Sciences (SPSS), version 11. Results are presented as mean ± SD. Statistical significance and difference from control and test values were evaluated by Student's *t*-test.

Results

The results are presented in Table 1. The systolic and diastolic blood pressures were found to be significantly higher ($P < 0.05$) in diabetic nephropathy patients who were smokers as compared to nonsmokers and controls. More obese persons were found in the smoker group than in the nonsmoker or control groups [Table 1]. Significantly poorer glycemic control ($P < 0.05$), as assessed by raised blood glucose and HbA_{1c} levels, was observed in smokers with diabetic nephropathy than in the nonsmokers with diabetic nephropathy or the controls. Impaired renal function (elevated levels of serum urea and creatinine) and significant ($P < 0.05$) decline in GFR was seen in

Table 1: Comparison of physical parameters, glycemic control, renal function, lipid profile, and acute phase response in nonsmokers and smokers as compared to controls

Parameters	Controls	Nonsmokers	Smokers
Systolic BP (mmHg)	123.77 ± 8.77	140.85 ± 11.37*	154.87 ± 12.48*†
Diastolic BP (mmHg)	78.73 ± 4.11	89.53 ± 7.2*	95.67 ± 7.76*†
BMI (kg/m^2)	21.35 ± 2.56	35.4 ± 2.15*	42.38 ± 3.15*†
Blood glucose (mmol/l)	5.4 ± 0.45	9.16 ± 3.05*	12.26 ± 4.16*†
HbA_{1c} (%)	4.59 ± 1.38	8.2 ± 1.84*	12.5 ± 3.6*†
Serum urea (mmol/l)	10.58 ± 2.63	15.42 ± 4.73*	18.19 ± 4.9*†
Serum creatinine (μmol/l)	107.67 ± 24.8	148.43 ± 37.8*	175.9 ± 46.84*†
GFR (ml/min)	79.13 ± 14.5	44.9 ± 11.58*	21.35 ± 7.4*†
Triglyceride (mmol/l)	0.97 ± 0.18	1.55 ± 0.24*	1.65 ± 0.21*†
Cholesterol (mmol/l)	4.83 ± 0.57	6.85 ± 0.83*	10.09 ± 1.26*†
LDL-cholesterol (mmol/l)	2.57 ± 0.42	3.25 ± 0.4*	4.8 ± 0.8*†
HDL-cholesterol (mmol/l)	1.34 ± 0.19	0.79 ± 0.14*	0.58 ± 0.1*†
Serum sialic acid (mmol/l)	1.72 ± 0.36	2.08 ± 0.41*	2.21 ± 0.39*†

*$P < 0.01$ as compared to controls; †$P < 0.05$ as compared to nonsmoker diabetic nephropathy patients

smokers with diabetic nephropathy as compared to the nonsmokers and controls. A more adverse lipid profile, as represented by significantly increased ($P < 0.05$) levels of serum triglyceride, cholesterol, and LDL-cholesterol and significantly ($P < 0.05$) decreased HDL-cholesterol, was also seen in diabetic nephropathy patients who were smokers as compared to nonsmokers and controls. Acute phase response and accumulation of proinflammatory molecules was also observed, as significantly raised ($P < 0.05$) levels of serum sialic acid were found in diabetic nephropathy patients who smoked as compared to the nonsmokers and controls.

Discussion

This study provides some insight into the biochemical changes induced by smoking on renal functions in diabetic nephropathy patients. Smoking causes intense sympathetic excitation which is reflected by the increase in blood pressure observed during the present study [Table 1]. This condition will certainly lead to tachycardia and increased concentration of catecholamines in the circulation.[16] Vasoconstriction, which causes an increase in renovascular resistance of about 11%, is noted as well. This is accompanied by a decrease in GFR.[17] The present study has also revealed a significant decrease in GFR in diabetic nephropathy patients who smoke as compared to those who do not smoke. Matters are somewhat complex in type 2 diabetes as compared to type 1 diabetes since smoking also increases the risk of developing type 2 diabetes, possibly because it increases insulin resistance.[18] Poor glycemic control, in terms of blood glucose level as well as HbA_{1c}, was observed in diabetic patients who were smokers. On the other hand it has been observed in previous studies[19] that in patients with diabetes who had near-normal HbA_{1c} and blood pressure, the rate of loss of measured GFR was considerably lower in ex-smokers as compared to current smokers. This suggests that benefit can be derived from cessation of smoking, even in patients with established diabetic nephropathy.

Smoking may induce albuminuria and abnormal renal function through advanced glycation end products (AGE's) as seen in this study. This process is also enhanced by the increased production, mobilization and circulation of lipid and lipid derivatives in the form of glycoconjugates as found in the presented study. AGE's are cross-linking moieties that form from the reaction of reducing sugars and the amino groups of plasma proteins, lipids and nucleic acids. It is known that the AGE's are responsible for enhanced vascular permeability[20] and they accelerate the vasculopathy of end-stage diabetic renal disease.[21] Recently it has been established that aqueous extracts of tobacco and cigarette smoke contain glycotoxins - highly reactive glycation products - that can rapidly induce *in vitro* and *in vivo* formation of AGE's.[22]

Insulin resistance may be another possible mechanism underlying the pathophysiologic effects of smoking-induced renal damage. Several investigators have found smoking to be causally related to insulin resistance in non-diabetic persons.[23-25] Insulin resistance has also been related to characteristic feature of syndrome, such as dyslipidemia, as shown in this study. Smoking may contribute to the development of diabetic complications through alterations in fat distribution,[5] which is associated with insulin resistance,[8] and a direct toxic effect on the beta cells. It has been shown that smoking cessation increases insulin sensitivity and improves the lipoprotein profile, despite a modest increase in weight.[26]

The mechanisms mentioned above might act through endothelial dysfunction; this is shown by the significant increase of serum sialic acid in smokers as compared to control as well as non-smoker diabetic patients. Acute phase response is created and pro-inflammatory molecules other than sialic acid, such as endothelin, prostacyclin, nitric oxide and cytokines, have also been found to be increased in smokers as compared to non-smokers in previous studies.[27-29]

From the observations and results of the present study it can be concluded that smoking increases the risk of albuminuria or proteinuria in the general population; there is also growing evidence to indicate that smoking increases the risk of renal function deterioration. There is clear evidence that smoking has adverse effects on the onset and evolution of diabetic nephropathy in type 1 and type 2 diabetes mellitus. Further studies are needed to assess the extent to which smoking counteracts the nephroprotective effects of treatment in diabetes mellitus.

Benefits of smoking cessation

In patients with type 1 diabetes and nephropathy who have adequate control of blood pressure, cessation of smoking significantly decreased urinary albumin excretion, although glycemia was not perfectly controlled.[30] In another study, progression of renal failure was found in 53% of current smokers but in only 33% of ex-smokers and 11% of nonsmokers.[19] It

is plausible that this is also true in nondiabetic renal disease. The present data do not allow us to assess the magnitude of the renal benefit derived from smoking cessation. When the above data and the clear negative impact of smoking on the course of renal function in diabetic patients with renal disease is taken into account, it is rational to conclude that smoking cessation is one of the single most effective measures to retard the progression of renal failure.

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