The Role of Smoking as a Modifiable Risk Factor in Diabetic Nephropathy

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Abstract

Objectives: To study the relation of smoking and abnormal renal function in type 2 diabetes mellitus by estimating urine protein-creatinine ratio, blood urea, serum creatinine, glomerular filtration rate and serum lipid profile in selected subjects.

Methods: Diabetic patients who attended the Diabetic Clinic, Medical College, Kozhikode were enrolled in the study. The study duration was 6 months, from July 2008 to December 2008. It was conducted in four groups of 40 subjects: diabetic smokers, diabetic non-smokers, non-diabetic smokers and non-diabetic non-smokers. The parameters assayed were: Blood urea, Serum creatinine, Fasting Blood Glucose and Serum Lipid Profile. The parameters assayed in the different groups were compared. Logistic regression analysis was done to study the effect of smoking on renal function.

Results: The mean difference of Urine protein-creatinine ratio between diabetic smokers and non-diabetic smokers is statistically significant (0.46±0.21 vs 0.24±0.14, p<0.001). The mean differences of Blood Urea between all the groups are statistically significant. The mean difference of Serum Creatinine of diabetic smokers with non-diabetic smokers is statistically significant (1.2±0.5 vs 0.96±0.2, p<0.05). The mean differences of Total Cholesterol, Triglycerides, HDL, LDL and VLDL between all the study groups is statistically significant. In the regression analysis, it was found that 12.9% of the alteration of renal function can be explained by smoking alone. (R2 = 0.129)

Conclusion: Smoking is an independent risk factor for progression of diabetic nephropathy. 24.8% of deterioration of renal function can be explained by smoking, obesity, hypertension and dyslipidemia and 12.9% of the alteration of renal function by smoking alone.

Introduction

Chronic kidney disease is a growing worldwide public health problem, because of its detrimental clinical outcome including end-stage renal disease and cardiovascular mortality and morbidity. Much evidence suggests that cigarette smoking is a strong and independent risk factor for kidney dysfunction in the general population and in diabetic patients. Patients with diabetes mellitus are the fastest growing population reaching end stage renal failure. Therefore, the impact of smoking on the rate of progression is of particular importance.

Editorial Viewpoint

- Smoking increases risk of progression to ESRD in diabetic patients as an independent factor.
- This cross-sectional study should be endorsed by a prospective observational long-term study.

Smoking has been shown to promote the progression of all stages of diabetic nephropathy. It increases the risk for the development of microalbuminuria and macroalbuminuria resulting in end stage renal failure. Smoking accelerates mortality in diabetic patients. It has been documented that a glomerular filtration rate of <60 ml and a minor increase of albumin excretion increases the cardiovascular risk 2 to 3 times. In a study conducted by Sawicki et al, it was proved that progression of nephropathy was less common in nonsmokers (11%) than in smokers (53%) and patients who had quit smoking (33%). The risk factors for developing chronic kidney disease may include hypertension, obesity, hyperglycemia, dyslipidemia and smoking. The identification of progression promoters is important for the creation of new powerful treatment modalities impeding the development of end-stage renal disease.
Table 1: Comparison of variables between diabetic smokers, diabetic non-smokers, non-diabetic smokers and non-diabetic non-smokers

<table>
<thead>
<tr>
<th>Variable</th>
<th>Normal value</th>
<th>Diabetic smoker A</th>
<th>Diabetic non-smoker B</th>
<th>Non-diabetic smokers C</th>
<th>Non-diabetic non-smokers D</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urine P/C ratio</td>
<td>&lt;0.2</td>
<td>0.46±0.21</td>
<td>0.35±0.28</td>
<td>0.24±0.14</td>
<td>0.19±0.12</td>
<td>0.099</td>
</tr>
<tr>
<td>Blood urea (mg/dL)</td>
<td>15-40</td>
<td>39.45±12.1</td>
<td>29.72±5.01</td>
<td>30.74±13.1</td>
<td>25.8±14</td>
<td>0.000†</td>
</tr>
<tr>
<td>Serum creatinine (mg/dL)</td>
<td>0.5-1.5</td>
<td>1.2±0.5</td>
<td>1.02±0.41</td>
<td>0.96±0.2</td>
<td>0.9±0.14</td>
<td>0.137</td>
</tr>
<tr>
<td>GFR (mL/min)</td>
<td>&gt;90</td>
<td>78.69±20.1</td>
<td>82.95±26.2</td>
<td>85.83±16.55</td>
<td>90.16±12.3</td>
<td>1.000</td>
</tr>
<tr>
<td>FBG (mg/dL)</td>
<td>70-110</td>
<td>169.05±62.26</td>
<td>160.6±54.80</td>
<td>91.85±5.41</td>
<td>89.5±7.36</td>
<td>1.000</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>100-140</td>
<td>137.65±6.53</td>
<td>134.75±9.13</td>
<td>133.55±6.19</td>
<td>130.6±7.22</td>
<td>0.479</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>60-90</td>
<td>90.75±6.11</td>
<td>88.45±7.94</td>
<td>87.1±5.16</td>
<td>84.95±3.82</td>
<td>0.515</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>18.5-25</td>
<td>25.59±2.48</td>
<td>23.8±2.72</td>
<td>24.02±1.32</td>
<td>23.41±1.84</td>
<td>0.000†</td>
</tr>
<tr>
<td>Serum cholesterol (mg/dL)</td>
<td>150-200</td>
<td>244.78±24.59</td>
<td>198.7±20.12</td>
<td>204.45±20.73</td>
<td>167.95±24.49</td>
<td>0.000†</td>
</tr>
<tr>
<td>HDL (mg/dL)</td>
<td>30-70</td>
<td>30.03±6.07</td>
<td>35.52±0.9</td>
<td>32.25±6.48</td>
<td>42.47±33.37</td>
<td>0.000†</td>
</tr>
<tr>
<td>LDL (mg/dL)</td>
<td>60-160</td>
<td>183±24.67</td>
<td>138.4±20.53</td>
<td>146.7±22.52</td>
<td>107.18±27.51</td>
<td>0.000†</td>
</tr>
<tr>
<td>VLDL (mg/dL)</td>
<td>10-30</td>
<td>31.75±7.13</td>
<td>24.78±4.29</td>
<td>25.45±3.11</td>
<td>18.3±6.77</td>
<td>0.000†</td>
</tr>
<tr>
<td>TG (mg/dL)</td>
<td>70-150</td>
<td>154.95±31.74</td>
<td>126.62±21.05</td>
<td>128±15.51</td>
<td>91.05±33.37</td>
<td>0.000†</td>
</tr>
</tbody>
</table>

†Statistically significant

Materials and Methods

Diabetic patients who attended the Diabetic Clinic, Medical College, Kozhikode were enrolled in the study. The study duration was 6 months, from July 2008 to December 2008. It was a cross sectional study conducted in four groups of 40 subjects namely diabetic smokers, diabetic non-smokers, non-diabetic smokers and non-diabetic non-smokers with prior written informed consent. The study was approved by the Institutional Ethics Committee. The smoker group consisted of those who smoked at least 1 cigarette/day for a minimum of 2 years. Diabetic patients of age 40-60 years with less than 5 year duration of disease were enrolled in the study. Subjects who did not have any history of diabetes mellitus, not on any antidiabetic drug, with fasting blood glucose <100 mg/dL, PPBS <140 mg/dL, HbA1c <6.5% were taken as controls. As the females who attended the diabetic clinic were non-smokers, only males were included in the present study. Patients with history of pre-existing primary renal disease were excluded.

Detailed history was taken with a structured questionnaire which included age, history of diabetes mellitus, hypertension, kidney disease, other comorbidities, and smoking history. Body weight and height were measured. Body mass index was calculated using the formula BMI = Weight (kg)/ Height² (meter).

Blood pressure was measured with a standard mercury sphygmomanometer while the patient was sitting after resting for 10 minutes and a mean of 3 readings was recorded. Urine samples were collected in sterile bottles for estimating urine microprotein and urine creatinine. Urine microprotein was estimated by pyrogallol red method and urine creatinine by Modified Jaffe’s Reaction. Urine microprotein-creatinine ratio was then calculated from microprotein and urine creatinine.

Glomerular filtration rate was calculated from serum creatinine by Cockroft and Gault formula:

\[ \text{GFR} = \frac{140 \times \text{Age in Years}}{72 \times \text{S. creatinine (mg/dL)}} \]

The parameters assayed in the different groups were compared. Data were analyzed using computer software, Statistical Package for Social Sciences (SPSS) version 14. To elucidate the associations and comparisons between different parameters, ANOVA test was used. For all statistical evaluations, a two-tailed probability of value, < 0.05 was considered significant. Logistic regression analysis was done to study the effect of smoking on renal function. Blood urea, serum creatinine, GFR, urine protein/creatinine were the parameters for assessing the renal function. The confounding factors included were hypertension, obesity, total cholesterol and triglyceride levels.

Results

The baseline characteristics of the group were matched with respect to age and gender. Statistical analysis was done to compare the parameters assayed in the four different groups: diabetic smokers, diabetic nonsmokers, non-diabetic smokers and non-diabetic nonsmokers. On comparison of variables between diabetic smokers and diabetic non-smokers (Table 1), the mean differences of blood...
Discussion

Smoking has emerged as an important modifiable risk factor for the development of diabetic and non-diabetic renal disease, accelerating the evolution from microalbuminuria, proteinuria, elevation of serum creatinine and progression to end stage renal disease. The consequences of cigarette smoking for patients with chronic kidney disease could be detrimental, as it affects progression of chronic kidney disease and cardiovascular disease. However, this is not sufficiently acknowledged by physicians and patients with chronic kidney disease.

In the present study, microproteinuria was quantified by finding the urine protein-creatinine ratio. There was an increase in urine protein-creatinine ratio in diabetic smokers compared to diabetic nonsmokers. The ratio was also increased in nondiabetic smokers than in nondiabetic nonsmokers (Table 1). The results obtained were similar to those in studies by Halimi et al. Smoking may induce proteinuria and abnormal renal function through advanced glycosylation end products (AGE’s). This process is also enhanced by the increased production, mobilization and circulation of lipid and lipid derivatives in the form of glycocalyx and nucleic acids. AGE’s are cross-linking moieties that are formed 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 and they accelerate the vasculopathy of end-stage diabetic renal disease.

There was a significant increase in blood urea levels in diabetic smokers compared to diabetic nonsmokers. Also the levels were increased in nondiabetic smokers compared to nondiabetic nonsmokers (Table 1). The findings were similar in studies by Shahid et al. There was an increase in serum creatinine levels in diabetic smokers compared to diabetic nonsmokers (Table 1) and in nondiabetic smokers compared to nondiabetic nonsmokers (Table 1). The results were consistent with those obtained in studies by Regalado et al.

A number of circulating and local vasoactive factors like endothelin-1 and angiotensin-1 were found to be increased in smoking subjects. These contribute to the impairment of renal function and elevation of urea and creatinine. Blood pressure and heart rate are increased by smoking mainly due to the action of nicotine. Increased Blood pressure is also one of the most important factors promoting progression of Chronic Kidney Disease.

The Glomerular Filtration Rate in diabetic smokers were found to be less than in diabetic nonsmokers (Table 1). GFR was also decreased in nondiabetic smokers compared to nondiabetic nonsmokers (Table 1). According to Shahid et al, the mediators released by nicotine cause vasoconstriction, which in turn causes an increase in renovascular resistance. This is accompanied by a decrease in GFR.

The urine protein-creatinine ratio, blood urea and serum creatinine were found to be increased in diabetic smokers than in nondiabetic smokers. Also the GFR is lower in diabetic smokers (Table 1). The pathogenesis of diabetic nephropathy is related to chronic hyperglycemia. The mechanisms by which chronic hyperglycemia leads to End Stage Renal Disease

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**Table 2: Significance of variables that affect renal function in type 2 diabetes mellitus**

<table>
<thead>
<tr>
<th>Variable</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking</td>
<td>0.001†</td>
</tr>
<tr>
<td>Systolic BP</td>
<td>0.004†</td>
</tr>
<tr>
<td>BMI</td>
<td>0.725</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>0.001†</td>
</tr>
<tr>
<td>Triglyceride</td>
<td>0.064</td>
</tr>
</tbody>
</table>

†Statistically significant
(ESRD) may involve the effects of soluble factors like growth factors, angiotensin II, endothelin and AGES. Hemodynamic alterations in the renal microcirculation like glomerular hyperfiltration or hyperperfusion and increased glomerular capillary pressure may be found in diabetic patients. Structural changes in the glomerulus like increased extracellular matrix, basement membrane thickening, mesangial expansion and fibrosis may also contribute to development of ESRD.

Compared to diabetic nonsmokers, diabetic smokers had higher mean FBG values. Also FBG levels were increased in nondiabetic smokers compared to nondiabetic nonsmokers (Table 1). Smoking causes increased release of catecholamines. Catecholamines, by activation of phosphorylase enzyme, cause glycogenolysis. They also inhibit insulin secretion. Several investigators have found smoking to be causally related to insulin resistance in nondiabetic subjects. Catecholamines may reduce the number of insulin binding sites as well as decrease the synthesis of glucose transporters.

The mean values of Total cholesterol, LDL, VLDL and Triglycerides were significantly higher in diabetic smokers than in diabetic nonsmokers (Table 1). The mean values of HDL were significantly lower in diabetic smokers compared to diabetic nonsmokers (Table 1). All these values except the HDL values were significantly higher in nondiabetic smokers compared to nondiabetic nonsmokers (Table 1). A clinical study by NS Neki also showed significantly higher values of LDL, VLDL, total cholesterol and triglycerides for smokers compared to nonsmokers. Nicotine stimulates sympathetic adrenal system leading to increased secretion of catecholamines. Catecholamines increase the activity of hormone sensitive lipase resulting in increased lipolysis and increased concentration of plasma free fatty acids (FFA). This results in increased hepatic triglycerides along with VLDL-Cholesterol in the blood stream. The serum cholesterol and lipoproteins except HDL were found to be elevated in diabetic smokers compared to nondiabetic smokers. Some of the possible reasons of higher concentration of serum cholesterol in diabetes may be attributed to obesity, increased calorie intake, decreased muscular exercise or inhibition of cholesterol catabolism. It has been suggested that the increase in triglyceride may be due to insulin deficiency which results in faulty glucose utilization and hyperglycemia. The fatty acids from adipose tissue are mobilized for energy purpose and excess fatty acids are accumulated in the liver which is converted to triglyceride. Insulin increases the number of LDL receptors, so chronic insulin deficiency might be associated with a diminished level of LDL receptor. This causes the increase in LDL particles and result in the increase in LDL cholesterol value in diabetes mellitus.

The diabetic smokers had higher systolic and diastolic blood pressure values than diabetic nonsmokers (Table 1) and nondiabetic smokers (Table 1). Systolic and diastolic blood pressure values were found to be higher among non-diabetic smokers than non-diabetic nonsmokers. (Table 1) Similar rise in blood pressure values were obtained for smokers in studies by Shahid et al and De Cosmo et al. This may be attributed to the intense sympathetic excitation and increased concentration of catecholamines in circulation. Nicotine increases plasma levels of vasopressin and endothelins and causes hypertension. Diabetes increases the risk of developing high blood pressure and other cardiovascular problems by adversely affecting the arteries, predisposing them to atherosclerosis and hypertension.

In the study, the BMI values were found to be high in diabetic smokers than diabetic nonsmokers and non-diabetic smokers (Table 1). Also, non-diabetic smokers had higher BMI values than non-diabetic non-smokers (Table 1). Similar high BMI values were obtained for smokers in studies by Shahid et al and Baggio et al. There is increasing evidence that smoking affects body fat distribution and that it is associated with central obesity and insulin resistance. Obesity and type 2 diabetes are causally linked. Fat accumulation induces insulin resistance through changes in hormonal secretions. Physical inactivity, both a cause and consequence of weight gain, also contributes to insulin resistance.

When the clear negative impact of smoking on the course of renal function in 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 progression of renal failure. Antismoking campaigns should be focused on achieving more success. For instance, banning smoking in public venues and at work places will decrease the deleterious effects of long-term exposure to nicotine.

Conclusions

Smoking is an independent risk factor for progression of diabetic nephropathy. 24.8% of deterioration of renal function can be explained by smoking, obesity, hypertension and dyslipidemia and 12.9% of the alteration of renal function by smoking alone. Smoking increases the risk of albuminuria or proteinuria and renal function deterioration. Smoking has adverse effects on the onset and evolution of diabetic nephropathy. There is enough evidence to advise patients with diabetes in general and diabetic kidney disease in particular to stop smoking and to alert about the increased risk that they face by continuing to smoke. Further studies are needed to
assess the extent to which smoking counteracts the nephro-protective effects of treatment in diabetes mellitus.

References


