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EFFECT OF CIGARETTE SMOKING ON RENAL FUNCTION IN HEALTHY MALE SUBJECTS, A CROSS-SECTIONAL ANALYTICAL STUDY

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ABSTRACT

Background: The increasing prevalence of chronic kidney disease (CKD) necessitates identification of all the possible risk factors. We conducted this study to determine the effect of smoking on renal function in healthy adults.

Methods: The study consisted of 40 healthy male subjects aged 31-40 years in each of the two groups: non-smokers and smokers (cigarettes only). The estimated glomerular filtration rate (eGFR) was calculated by the CKD-EPI equation (Chronic Kidney Disease Epidemiology Collaboration), and the urinary albumin creatinine ratio (ACR), was measured by nephelometry.

Results: The mean eGFR in non-smokers was 110.7±9.6 mL/min/1.73m^2 and 110.7±9.4 mL/min/1.73m^2 in smokers (p=0.999). Mean urinary ACR was significantly (p<0.001) higher in smokers (14.55±8.08 mg/g) as compared to non-smokers (7.96±2.86 mg/g). Further within smokers, there wasa positive correlation between pack years of smoking and urinary ACR values (r=0.858, p<0.001)

Conclusion: Cigarette smoking was associated with significantly higher urinary ACR in healthy young males.

KEYWORDS : urinary ACR, Glomerular filtration rate, Smokerlyzer, CKD-EPI

INTRODUCTION

Tobacco consumption has been directly linked to cardiovascular disorders, lung diseases and malignancies(1). Studies conducted in the patients with various renal pathologies such as diabetes, hypertension and other glomerulopathies have implicated smoking as an important renal risk(2)(3).

Shah H(4) while studying non-diabetic volunteers found urinary microalbumin to be 373 ± 13.9 mg/day in tobacco chewers compared to 93.6 ± 13.9 mg/day in non-tobacco users. In a two year follow up study conducted by Tozawa et al(5) the relative risk of developing proteinuria over the study period was 1.32(p=0.04) for smokers compared to non-smokers in non-diabetic and non-hypertensive subjets. However, these studies had several limitations including estimation of proteinuria by semiquantitative methods such as urine dipstick or were conducted without accounting for various other renal risk factors like obesity. Hence, data on the renal effects of tobacco use in healthy population are scarce.

We therefore undertook this study to assess the effects of cigarette smoking on renal parameters, eGFR and urinary microalbumin levels.

SUBJECTS AND METHODS

The cross-sectional analytical study was conducted in the Department of Medicine and the Department of Biochemistry of our institute over a period of 18 months from 2011-2013. Ethical clearance from the Institutional Ethical Committee for Human Research was taken.

Assuming a pooled standard deviation of 7.54 mg/g we required a sample size of 16 in each group to achieve a power of 80% and a level of significance of 5% for detecting a true difference in means between the smokers and non-smokers of 7.5 mg/g(6). The study population comprised of 80 successive apparently healthy male subjects aged 31 to 40 years, selected from among the attendants of patients visiting UCMS and GTBH. The subjects were recruited into the two groups:

Non-smokers: Subjects who denied use of any tobacco product (n=40)

SMOKERS:

Subjects who were current smokers at the time of enrolment (one or more cigarettes smoked per day on most of the days in the last 6 months from the time of enrolment) (n=40). Subjects consuming tobacco through means other than cigarette smoking were not included.

Each potential study subject underwent detailed history taking and relevant clinical examination. Hypertension, diabetes mellitus/ impaired glucose tolerance, obesity (BMI≥ 25 kg/m^2 and/or Waist circumference ≥ 90 cm)(7), use of nephrotoxic drugs and/ or hazardous alcohol consumption (21 drinks or more per week [1 drink = 10 g alcohol])(8) formed the exclusion criteria for our study. Urinary tract infection was excluded by urine microscopy and urine culture in each subject.

Bedfont Smokerlyzer was used to objectively test the smoking status of participants. It measured breath carbon monoxide (CO) levels in parts per million (ppm) based on the conversion of CO to carbon dioxide (CO_2) over a catalytically active electrode. On breath holding, the CO in the blood forms equilibrium with the CO in the alveolar air; therefore, there was a high degree of correlation between breath CO levels and COHb concentration. This enabled the Smokerlyzer to accurately estimate the blood COHb concentration from the breath CO level. The blood COHb was in turn proportional to the number of cigarettes smoked. A cut off level of 5 ppm was used to differentiate smokers from non-smokers(9).

10 mL of fasting peripheral venous blood was collected from subjects for various laboratory parameters including serum creatinine. eGFR was calculated using the CKD- EPI equation(10)

eGFR = 141 X min (Scr/,1)$^{\alpha}$ X max (Scr/,1) $^{-1.209}$ X (0.993)^{Age} X 1.018 (if female).

Where;Scr is serum creatinine (mg/dL)
=0.7 for females and 0.9 for males
α= -0.329 for females and -0.411 for males
min indicates the minimum of Scr/ or 1, and
max indicates the maximum of Scr/ or 1.

Estimation of urinary ACR: First voided morning urine sample of subjects was analyzed for urinary microalbumin by nephelometry. 20 µL of urine sample was mixed with 40 µL mALB antiserum and 400 µL of buffer solution in a cuvette using an electronic pipette. The principle involved was immunonephelometry, wherein the amount of light scattered by insoluble complexes formed by the reaction between urinary albumin and its antiserum was directly proportional to the amount of urine albumin and was expressed as mg/L of reagents. First voided urine sample was also analyzed for urine creatinine using Jaffe's reaction and results were expressed as g/L. The urinary ACR was calculated by the ratio of urine albumin to creatinine and expressed as mg/g.

STATISTICAL ANALYSIS

The mean of descriptive, anthropometric, and biochemical parameters in non-smokers and smokers were compared using unpaired 't' test at 5% level of significance. Analysis was done using SPSS version 20.0. In smokers, the comparison in terms of pack years smoked with respect to ACR was done in subgroups of ≤ 1 pack year and > 1 pack years of smoking history by unpaired 't' test. Spearman's Correlation analysis was performed in smokers to find the correlation of pack years of smoking with eGFR and urinary ACR. The distribution of subjects in non-smokers and smokers based on urinary ACR levels were compared using Chi square for trend.

RESULTS

The demographic and laboratory characteristics of study subjects is represented in the table I. The study subjects were comparable with respect to all these characteristics. The Smokerlyzer findings of study subjects are depicted in table II. The mean eGFR was 110.7±9.6 mL/min/1.73m^2 in non-smokers and 110.7±9.4 mL/min/1.73m^2 in smokers (p=0.999).

The mean urinary ACR was significantly lower in non-smokers (7.96±2.86 mg/g) compared to smokers (14.55±8.08 mg/g) (p<0.001) (Fig. 1). Further among non-smokers, only 6 (15%) out of 40 subjects had urine ACR >10 mg/g, whereas among smokers 25 (62.5%) out of 40 subjects had urine ACR >10 mg/g. Within the smokers, the urinary ACR was significantly higher in those with a cumulative smoking exposure of > 1 pack year (17.73±7.90 mg/g) compared to smokers who had ≤ 1 pack year (7.97±2.74 mg/g) of smoking history (p<0.001). The pack years of cigarette smoking showed a strong positive correlation with urinary ACR (r=0.858) (p<0.001) (Fig 2).

DISCUSSION

In the present study, we found the cigarette smokers to have a significantly higher urinary ACR levels compared to non-smokers with the similar eGFR. Our study was conducted in a healthy male population within a narrow age group of 31-40 years who were free of systemic conditions known to affect renal function. Halimi et al(11) while studying 28,409 volunteers from general population reported that the current smokers had a significantly higher creatinine clearance than non-smokers. De Cosmo et al(12) in a study of 316 Type 2 male diabetics demonstrated that smokers were more frequently affected by low GFR (< 60 mL/min/m^2) compared to non-smokers with an odds ratio of 2.2 which was independent of age, HbA1C, albuminuria, and dyslipidemia. In our cross-sectional study we came up with no significant effect of smoking on eGFR.

In contrast to the effects on eGFR, our study found a significant and positive correlation between degree of albuminuria and smoking exposure. Although the mean albuminuria was within the normal range of <30 mg/g of urinary ACR, it was significantly higher in smokers than in non-smokers. Microalbuminuria defined as 30 and 300 mg of urinary albumin in a 24-hour urine collection, has been identified as a newly recognized cardiovascular and renal risk factor in general population(13). It was later recognized that the risk of cardiovascular events and of progression to overt nephropathy was also elevated in subjects in the 'high normal' range of albuminuria(14). Data from Losartan Intervention For End point reduction in hypertension (LIFE)(15), and Framingham studies(16) clearly suggest that only negligible amounts of albuminuria below approximately 2 mg/g of urine creatinine (or an estimated excretion rate of 2 mg/day) should be considered as 'normal'. This led Ruggenenti et al(17) to suggest that among subjects with albuminuria, there is a continuous relationship between albumin excretion and risk of renal injury and no lower bound of urinary albumin could be identified which separates subjects at differential risk.

In support of our findings, previously reported studies (5), had confirmed the negative impact of smoking on proteinuria. However, these studies were hampered by various drawbacks such as use of semiquantitative estimations for proteinuria or were conducted in patients with pre-existing systemic disorders.

CONCLUSIONS

Cigarette smoking is associated with increased urinary ACR levels in healthy male subjects which is a well-established cardiovascular risk factor and an indicator of future progression of renal disease. We propose that utilisation of all the possible strategies at our disposal to curtail the use of tobacco in healthy general population could limit the development of smoking associated renal dysfunction.

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Table I: Demographics and laboratory parameters of non-smokers and smokers

Parameters	Non-smokers	Smokers	Significance (p value)
Age (years)	35.1±2.5	35.0±2.9	0.808
Waist circumference (cm)	83.9±3.7	84.2±4.5	0.860
Body mass index (kg/m2)	21.6±2.3	21.8±3.0	0.760
Systolic blood pressure (mm Hg)	114.4 ±9.3	116.1 ±8.6	0.393
Diastolic blood pressure (mm Hg)	73.6 ±7.4	74.2 ±7.0	0.597
Fasting blood sugar (mg/dL)	85.5±7.0	86.0±8.0	0.779
Post prandial blood sugar (mg/dL)	117.4±12.5	118.6±14.4	0.674
Hemoglobin (g/L)	14.3±1.4	14.6±1.2	0.358
Blood urea (mg/dL)	25.6 ±7.4	25.4 ±6.5	0.909
S. creatinine (mg/dL)	0.87±0.1	0.86±.1	0.757
Total cholesterol (mg/dL)	169.2±43.0	162.3±36.4	0.439
Low density lipoprotein (mg/dL)	102.3±34.7	99.5±29.7	0.700

Table II. Smokerlyzer findings in non-smokers and smokers

	Non-smokers	Smokers	Significance (p value)
Breath CO* (in ppm)	3.1±1.5	13.1±5.8	<0.001
COHb %**	1.1±0.2	2.7±0.9	<0.001

*CO -Carbon Monoxide
** CoHb- Carboxy Hemoglobin

Fig 1. Bar diagram showing mean urinary ACR levels in non-smokers and smokers

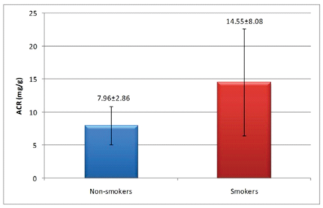
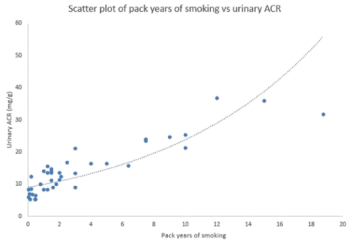


Fig 2: Scatter plot showing correlation of pack years of cigarette smoking with urinary ACR



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