The Relationship between Cigarette Smoking and Renal Function: A Large Cohort Study

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ABSTRACT: **Background:** Both cigarette smoking and chronic kidney disease (CKD) are linked to cardiovascular morbidity and development of atherosclerosis. However, the relationship between cigarette smoking and renal function is not clearly understood.

Objectives: To investigate the relationship between cigarette smoking and renal function, and determine whether the intensity of cigarette smoking influences renal function.

Methods: We conducted a retrospective analysis of subjects attending the screening center at the Rabin Medical Center. Subjects were classified as smokers, non-smokers and past smokers. Renal function was evaluated by means of the CKD-EPI equation for estimating glomerular filtration rate (eGFR). Multivariate and gender-based analyses were performed.

Results: The study population comprised 24,081 participants, of whom 3958 (17%) were classified current smokers, and 20,123 non-smokers of whom 4523 were classified as past smokers. Current smokers presented a higher eGFR compared to the non-smoking group (100.8 vs. 98.7, $P < 0.001$) as well as higher rates of proteinuria (15.3% vs. 9.3%, $P < 0.001$). The difference in eGFR between smokers and non-smokers was more significant in males than in females. Past smokers had the lowest eGFR of all groups; this difference remained significant after age adjustments ($P = 0.005$).

Conclusions: Cigarette smoking is associated with higher eGFR compared to non-smoking. This difference was more pronounced in males than females, implying a gender-based difference. The higher prevalence of proteinuria in smokers suggests a mechanism of hyperfiltration, which might result in future progressive renal damage.

IMAJ 2016; 18: 553–556

KEY WORDS: cigarette smoking, chronic kidney disease (CKD), glomerular filtration rate (GFR), proteinuria, hyperfiltration

Cigarette smoking has long been a global health issue and is a well-known cause of many pathologies, such as cardiovascular morbidity, cancer evolution and pulmonary diseases. Recent data estimate that approximately 20% of the total world adult population are current smokers. Tobacco use is a leading cause of preventable death. In the United States, an estimated annual mortality of 443,000 is attributed to smoking, including nearly 161,000 deaths from cancer, 128,000 from cardiovascular diseases, and 103,000 from respiratory diseases [1,2].

Chronic kidney disease (CKD) is a major health issue associated with increased mortality and decreased quality of life. The effect of cigarette smoking on renal function had previously been linked to long-term end-stage kidney disease (ESKD), with ESKD more common in smokers; its influence on healthy adults has yet to be determined [3]. Previous studies point to a lower estimated glomerular filtration rate (eGFR) in diabetic patients who smoke compared to non-smoking diabetics [4], but firm data of healthy populations are sparse and conflicting [5,6]. The presence of microalbuminuria in diabetic patients is considered a marker of diabetic nephropathy, and its presence in non-diabetic individuals is linked to increased risk of cardiovascular disease [7]. Recent studies suggest a higher prevalence of microalbuminuria in smokers compared to non-smokers, and raise the possibility that renal glomerular injury and hyperfiltration are mechanisms of renal injury in smokers [8].

In the current study, we investigated the relationship between cigarette smoking and renal function in a large Israeli cohort in order to determine whether the intensity of cigarette smoking influences renal function.

PATIENTS AND METHODS

A community-based cohort study was conducted retrospectively on a referral center database at the Rabin Medical Center, Israel. The data collected during 2000–2013 comprised approximately 20,000 subjects with an age range of 20–80 years, mainly employees of various companies. Each subject underwent a thorough medical history evaluation, complete physical examination, and a series of blood and urine tests.

CIGARETTE SMOKING DETERMINATION

Subjects were questioned regarding their smoking habits and were classified as non-smokers, current smokers and past smokers. Current smokers were further divided according to the "intensity" of their smoking: patients with less than 10 pack-years, 10–20 pack-years and more than 20 pack-years [9]. Patients who smoked in the past but did not smoke at the time of the last visit were classified as "past smokers" and were excluded from most of the analyses.

RENAL FUNCTION DETERMINATION

Renal function was evaluated by glomerular filtration rate estimation (eGFR) using the CKD-EPI equation, which has been shown to provide a more accurate estimate of GFR among individuals with normal or near-normal GFR compared to the Cockcroft-Gault or MDRD equations [10].

PROTEINURIA DETERMINATION

Urine samples were collected as clean-catch, mid-stream, and random urine specimens. The results of dipstick urinalysis were interpreted as negative or positive (≥ 25 mg/dl); the exact amount of protein in the urine was disregarded for the purpose of our study.

STATISTICAL ANALYSIS

We compared eGFR and proteinuria between smokers and non-smokers, and calculated the eGFR for the different smoking groups. A gender-based comparison was performed as well. Categorical variables were compared using Fisher's exact test. Continuous variables were presented as means (± SD) or medians (interquartile range, IQR) when appropriate, and compared using Student's *t*-test and the Mann-Whitney U test respectively. When more than two groups were compared (e.g., smokers, past smokers and non-smokers), ANOVA was employed to compare normally distributed data, and for non-normal data we used the Kruskal-Wallis test. Logistic regression analysis was used to assess the odds ratio (OR) of proteinuria in smokers compared to past smokers and current smokers (the reference category). Model 1 presents the crude association; Model 2 is adjusted for age, hypertension, diabetes mellitus (DM), low density lipoprotein-cholesterol (LDL-C), high density lipoprotein-cholesterol (HDL-C) and triglycerides.

Table 1. Baseline characteristics of the study population

Smoking status	Current smoker	Never smoked	Past smoker	Total	*P* value
N	3958	15,600	4523	24,081	
Age at baseline (years)	44.2 ± 10.1	45.2 ± 10.2	50.1 ± 10.7	46 ± 10.4	< 0.001
Female gender, n (%)	1330 (33.6%)	5334 (34.2%)	1055 (23.3%)	7719 (32.1%)	< 0.001
Hypertension, n (%)	272 (6.9%)	1383 (8.9%)	652 (14.4%)	2307 (9.6%)	< 0.001
Diabetes mellitus, n (%)	170 (4.3%)	430 (2.8%)	262 (5.8%)	862 (3.6%)	< 0.001
Body mass index (kg/m²)	26.4 ± 4.4	26.3 ± 4.2	27.7 ± 4.3	26.6 ± 4.3	< 0.001
LDL-C (mg/dl)	121.5 ± 33	117.7 ± 30.3	119.1 ± 31	118.6 ± 30.9	< 0.001
HDL-C (mg/dl)	49.4 12.5	51.9 12.9	50.7 ± 12.4	51.3 ± 12.8	< 0.001
Triglycerides (mg/dl)†	116 (84–166)	103 (74–145)	114 (83–166)	107 (77–152)	< 0.001
eGFR (ml/min/1.732 m²)	100.8 ± 13.9	98.7 ± 14.3	94.9 ± 14.3	98.3 ± 14.3	< 0.001
Urine albumin › 25 mg/dl	482 (15.3%)	1207 (9.3%)	394 (10.5%)	2083 (10.5%)	< 0.001

Data are expressed as mean ± standard deviation, n(%) or median† (interquartile range)
eGFR = estimated glomerular filtration rate, LDL-C = low density lipoprotein-cholesterol, HDL-C = high density lipoprotein-cholesterol

Multiple linear regression analysis was used to assess the effect of smoking status on GFR adjusting for age, hypertension, diabetes, LDL-C, HDL-C and triglycerides.

All reported *P* values are two-sided; a *P* value of 0.05 was chosen to indicate statistical significance. All analyses were conducted using R: A Language and Environment for Statistical Computing, version 3.1.1 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

The study population comprised 24,081 participants who attended the referral center from 2000 to 2013, of whom 3958 (17%) were classified as current smokers; 20,123 did not smoke including 4523 patients classified as past smokers. Current smokers smoked for a median of 15 pack-years (IQR 6–25). For past smokers, the median time of smoking cessation was 10 years (IQR 5–20), and the median smoking duration was 10 pack-years (IQR 5–20). The main characteristics of the study population are presented in Table 1. Median age was 45 years both in the smokers group and the non-smokers group, while the past smokers group had a median age of 50 years. There were no differences in smoking status between males and females (17% current smokers). The smokers and past smokers displayed a higher prevalence of diabetes mellitus, higher levels of LDL-C and triglycerides and lower levels of HDL-C, compared to the non-smoking group. Hypertension, on the other hand, was more common in the non-smoking and past-smoking group compared to current smokers. Women had a higher eGFR than males, a finding that may be explained by the use of the CKD-EPI equation, which is known to produce a slightly higher eGFR in females [10].

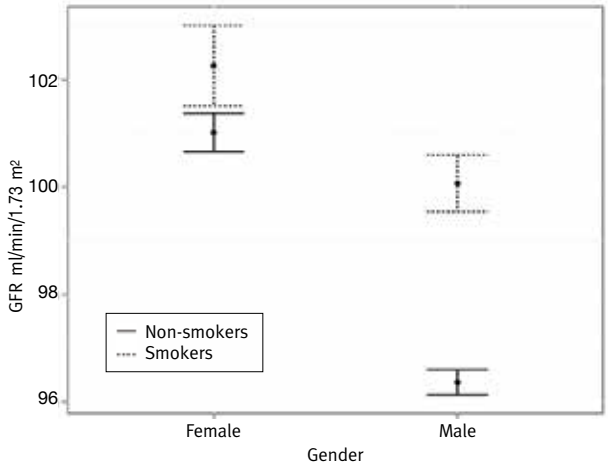
With regard to renal function, the smoking group presented a higher eGFR compared to the non-smoking group (100.8 ml/min vs. 98.7, $P < 0.001$), as well as higher rates of proteinuria (15.3% vs. 9.3%, $P < 0.001$) [Table 1]. These differences remained significant for both males and females after multivariate analysis comprising age, gender, DM, hypertension, HDL-C, LDL-C and triglycerides [Figure 1]. Odds ratio for developing proteinuria was higher in smoking males and females [Table 2]. The difference in eGFR between smokers and non-smokers was more significant in the male group compared to the female group [Figure 1].

Figure 2 shows the relation between eGFR and intensity of smoking. Although in a univariate analysis the heavier smokers had lower eGFR, the differences were not significant after age adjustment. Past smokers, however, had the lowest eGFR of all groups (94.9 ml/min). This difference remained significant after age adjustments ($P = 0.005$).

DISCUSSION

Little is known about the effects of cigarette smoking on renal function, and the few studies examining this relationship show

Figure 1. Glomerular filtration rate (GFR) and smoking in men and women



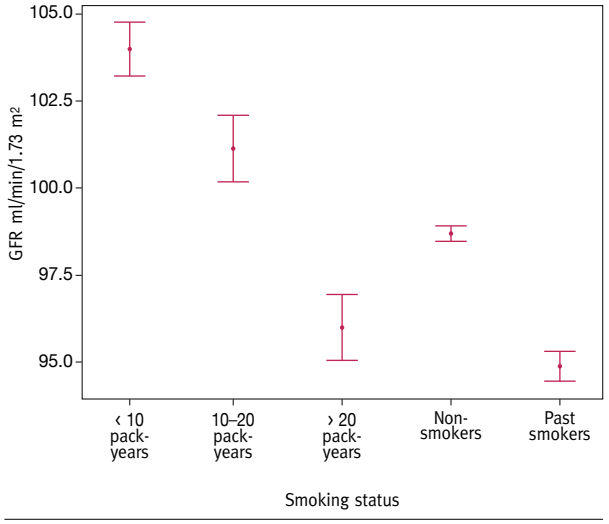
	Current smokers	Never smoked	All	*P* value
Males	100.07	96.36	97.0	< 0.001
Females	102.26	101.02	101.23	0.003

Table 2. Odds ratio (OR) for proteinuria in the different smoking groups

	Current smokers	Never smoked	*P* value
Males			
Crude OR (95%CI)	1	0.6 (0.52–0.69)	< 0.001
Adjusted* OR (95%CI)	1	0.62 (0.54–0.72)	< 0.001
Females			
Crude OR (95%CI)	1	0.53 (0.43–0.65)	< 0.001
Adjusted* OR (95%CI)	1	0.53 (0.43–0.66)	< 0.001

*Adjusted for age, diabetes mellitus, hypertension, low density lipoprotein-cholesterol and high density lipoprotein-cholesterol, and triglycerides

Figure 2. The relation of glomerular filtration rate (GFR) to smoking status and intensity of smoking



conflicting results. Our study found an association between cigarette smoking and elevated eGFR that was more significant in males. Additionally, proteinuria was significantly more common among smokers.

Previous studies in healthy Asian subjects support our finding that cigarette smoking is associated with a higher eGFR, possibly due to hyperfiltration as the main mechanism [8,9]. However, other studies failed to show this association [6].

Our study was performed in a large cohort, the majority being healthy adults. In contrast to previous studies, mainly Asian populations in which the incidence of smoking males is very high (around 45%) and the incidence of smoking females low, our study population reflects the average smoking status in the Western world. In our study, the rate of smoking was similar in males and females. The vast majority of our study population was free of medical conditions that may have confounded our results. Nonetheless, a multivariate analysis for age, gender, DM, hypertension, HDL-C, LDL-C and triglycerides was performed to ensure the significance of our results. When assessing eGFR we employed the CKD-EPI equation, which was shown to perform better than the MDRD (Modification of Diet in Renal Disease) equation, especially at higher GFR, with less bias and improved precision [10]

Interestingly, the past smokers group exhibited the lowest eGFR of all groups, implying that current smoking elevates the eGFR through unknown mechanisms, possibly hyperfiltration, but once smoking is discontinued the eGFR actually declines due to the disappearance of the hyperfiltration state and the evolution of long-term kidney damage. A possible mechanism for the effect of smoking on renal function might be related to cyclic GMP levels, which are higher among smokers than non-smokers [11]. Elevated levels of urinary cyclic GMP, which may occur due to nicotine exposure, might have caused renal vasodilation and therefore elevated the eGFR [12]. This possible mechanism may also explain the lower likelihood of systemic hypertension in smokers compared to non-smokers in our study.

In our study, eGFR in smokers was significantly higher than in non-smokers. This effect was more pronounced in males, suggesting a gender-based difference. Such differences have been described previously, although to a lesser extent [7].

Furthermore, the risk for the development of proteinuria was more common in smoking males than in smoking females [Table 2]. Therefore, smoking males were more likely to have a higher eGFR with abnormal urinary protein level compared to non-smoking males, and smoking females displayed this effect but to a lesser extent.

Regarding the intensity of smoking according to pack-years, Figure 2 shows that the heavier the smoking the lower the eGFR; however, this difference is probably attributed to the age difference between the groups, since after adjustments for age, diabetes and hypertension, the difference was not significant. One might have expected that with heavier smoking there will

be a higher eGFR. However, this "reverse effect," where a trend towards lower eGFR in the heaviest smokers is shown, might be related to a late effect of cigarette smoking. Hence, cigarette smoking elevates the eGFR acutely, possibly due to a hyperfiltration state, yet with time this effect declines and might even decrease eGFR.

Our study has several limitations. As a retrospective study, certain biases might have occurred. Most of the study participants were males (68%). We lacked information regarding medication use, yet the vast majority of our study population were healthy young adults sent by their employers to undergo routine checkups and therefore were less likely to take medications. The group of past smokers had higher rates of metabolic diseases (diabetes, hypertension). One may assume the cause for smoking cessation might have been related to complications arising from their metabolic diseases. Lastly, urine protein level was measured by a spot urine test, a method considered more accurate than albumin-to-creatinine ratio.

In conclusion, our study showed that cigarette smoking elevates eGFR in healthy adults compared to non-smokers, and also elevates the occurrence of proteinuria. This effect was more pronounced in males than in females. The physiological mechanism of this phenomenon is not yet clear, and future studies in other populations are recommended to support these findings. The intensity of smoking (pack-years) did not show a significant influence on eGFR, though heavy smokers exhibited a trend towards lower eGFR when compared with light smokers. The past-smoking group had the lowest eGFR of all groups, possibly due to the disappearance of a hyperfiltration state. Future longitudinal studies are required to evaluate whether eGFR elevation as observed in our study in current smokers is maintained into the future or is associated with renal function deterioration over the long term. Furthermore, further basic science studies are required to unmask the mechanisms underlying the influence of cigarette smoking on renal function.

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