

Smoking and the Kidney

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SUMMARY

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.

Smoking disturbs renal haemodynamics. An important role of endothelial cell dysfunction has been documented in acute and chronic studies.

In a retrospective case control study we document the strikingly elevated risk of progressing to end stage renal disease in smokers with immune (glomerulonephritis) and non immune (ADPKD) renal diseases. Mainly vascular lesions underlie the accelerated progression.

There is evidence that the renal risk is less in ex-smokers than in current smokers, emphasising the need to advise renal patients to stop smoking.

Key words: smoking, diabetic nephropathy, sympathetic overactivity, endothelin, microalbuminuria, chronic kidney disease.

INTRODUCTION

Smoking and cigarette smoking in particular, is one of the most important modifiable renal risk factors. In contrast to its well-documented likelihood of promoting carcinogenesis, lung disease and cardiovascular events, the renal risk associated with smoking has only recently attracted attention even in the renal community¹, although the renal risk conferred by smoking has been known to diabetologists for over 2 decades².

ACUTE EFFECTS OF SMOKING ON THE KIDNEY

As early as 1907 Hesse described in his doctoral thesis the transient increase of blood pressure and heart rate during cigarette smoking³. This notwithstanding, it had long been claimed that there was no excess hypertension in smokers⁴, with presumably hypertension being masked as the body weight of smokers is low. Cryer *et al*⁵ documented marked sympathetic activation during cigarette smoking and the release of blood pressure active hormones such as AVP, aldoster-

Received for publication: 26/06/2006

Accepted: 24/07/2006

one, cortisone and ACTH. The effect of smoking on blood pressure outlasts the period of smoking. In a controlled study Ritz documented higher night time blood pressure on a day when occasional smokers smoked compared to a day when they did not smoke (Figure 1)⁶. She found that this was accompanied by commensurate changes in heart rate. The effects of smoking are complex, as illustrated by the findings that smoking also increases arterial stiffness⁷ and causes a curious “reversed” office hypertension, i.e. normal office blood pressure in patients with high home blood pressure measurements⁸.

The effects of smoking on renal haemodynamics are pronounced. Ritz *et al* showed that smoking causes an acute increase in circulating epinephrine, in heart rate and in blood pressure. This is accompanied by a decrease in the filtration fraction with a significant increase in renal vascular resistance⁹. This renal haemodynamic pattern could be repro-

duced in healthy volunteers by chewing gum containing nicotine, suggesting that nicotine is the main culprit. Interestingly, in patients with IgA glomerulonephritis, smoking failed to consistently reduce the filtration fraction; on average the filtration fraction remained unchanged and a transient increase in urinary albumin excretion was seen, consistent with (but not proof of) acute glomerular hypertension. Plasma renin activity in the circulation did not increase, but even this is inappropriate to the blood pressure increase. Nevertheless, the renin-angiotensin system may play a role in the genesis of the acute haemodynamic changes in the kidney, since they were abrogated by β -1 selective blockers¹⁰.

In animal experiments Odoni *et al* found severe proteinuria, pronounced glomerulosclerosis and marked interstitial fibrosis were produced when an acetone extract of cigarette smoke was applied to the oral mucosa of subtotaly nephrectomized rats¹¹.

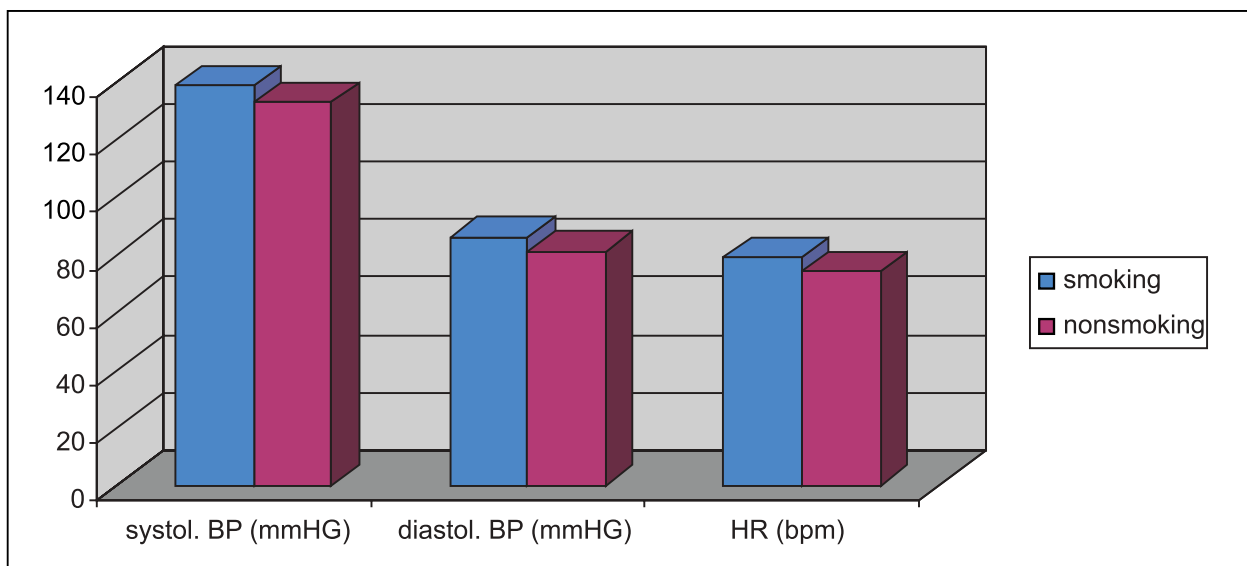


Figure 1: Systolic and diastolic blood pressure as well as heart rate in healthy occasional smokers – comparison of a smoking day (blue) with a non-smoking day (red) (Ritz S., ref.6)

Despite these acute alterations of glomerular function and morphology, in the long run the damage from smoking seems to be mainly mediated by damage to the renal vasculature. Halimi¹² found that cigarette smoking acutely increased the excretion of cGMP in the urine, pointing to compensatory vasodilatation in response to nicotine mediated vasoconstriction. In contrast, in long term observations, Gambaro¹³ found increased endothelin-1 concentrations in cigarette smokers and this was associated with increased renovascular resistance. The concept of a primary vascular problem in the kidneys of smokers is in line with the observation of Lhotta¹⁴ in his examinations of renal biopsies of patients with primary renal disease. In smokers he found more severe myointimal hyperplasia and arteriolar hyalinosis. The concept of primarily vascular damage is also in line with our recent observation¹⁵ that diabetic patients with microalbuminuria/proteinuria had a more rapid increase of serum creatinine concentration with time compared to non smokers despite there being no difference in urinary protein excretion.

SMOKING AND RENAL DISEASE

Diabetic nephropathy

Since the seminal description of Christensen², cigarette smoking had been known to diabetologists as a risk factor for the onset and progression of microangiopathy. Cigarette smoking diabetics have a higher risk of developing microalbuminuria, a greater rate of progression to proteinuria and a greater risk of experiencing an elevation of serum creatinine. This has been confirmed in numerous studies¹⁶⁻²¹. In diabetic patients with overt diabetic nephropathy and elevated serum creatinine, the measured rate of

loss of creatinine clearance was twice as high in smokers compared to non-smokers²². Obviously there are no controlled prospective studies on whether cessation of smoking attenuates the rate of loss of GFR, but the observation of Sawicki is telling²¹: the risk of progression of diabetic nephropathy in type I diabetic patients was 11 % in non-smokers, 33 % in ex-smokers and 53 % in current smokers, suggestive (but not proof) of a beneficial effect of cessation of smoking.

It is of interest that several recent studies confirm that smoking increases not only the risk of developing diabetic nephropathy but also the risk of developing type II diabetes, as found in the nurses' health study²³ and recently confirmed by others²⁴.

Non diabetic renal disease

While there have been some reports that the risk of progression is higher in patients with lupus nephritis who smoked²⁵ and in patients with ADPKD²⁶, it is uncertain, however, whether smoking affects the immune response and whether – in view of the two hit hypothesis concerning the genesis of renal cysts in ADPKD – the higher renal risk of smoking ADPKD patients could not be explained by smoking induced DNA mutations.

In a retrospective case control study, however, examining patients with inflammatory (IgA glomerulonephritis) or non-inflammatory (ADPKD) primary renal disease, Orth *et al*²⁷ found an increased odds ratio of progression to end stage renal disease in patients with 5 – 15 pack years [odds ratio 3.5 (1.3 – 9.6)] and in patients with > 15 pack years [5.8 (2.0 – 17.0; p < 0.001)]. Interestingly, the increased odds ratio was found only in patients who were not on ACE inhibitors (Table1).

Table 1

Smoking – ESRF in men (n=144) with primary renal disease (retrospective case-control study)

Pack-years	Odds ratio (95%-CL)	p
0-5	1.0	–
5-15	3.5 (1.3-9.6)	0.017
>15	5.8 (2.0-17.0)	0.001

Orth, *Kidney Int* (1998)54:926

ACE inhibitors do not provide complete protection, however. In type 2 diabetics Chuahirun found that despite treatment with ACE inhibitors reaching target blood pressure values, during a 61 months follow up serum creatinine had risen to significantly higher values in smokers (1.78 ± 0.2 mg/dl) compared to non-smokers (1.32 ± 0.01)²⁸.

The adverse effect of cigarette smoking on renal function was not seen only in patients with primary renal disease but also in renal allograft recipients²⁹. The hazard ratio of graft loss censored for patient death was 1.48.

American authors even describe as a distinct entity linked to hypertension and smoking the unique glomerular disease “idiopathic nodular glomerulosclerosis”³⁰. In a cohort with this disease, 91 % of the subjects were smokers with a total of 53 % ± 3 pack years. Renal histology showed mesangial sclerosis, basal membrane thickening, arteriosclerosis and arteriolosclerosis. After 26 months, 35 % of the patients had reached end stage renal disease.

The adverse effect of smoking on renal function in patients without renal disease has also been well documented. Smoking was the most powerful predictor of progression in patients with severe essential hypertension in the study of Regalado³¹ and in the study of Bleyer³².

Cigarette smoking also increased the risk of microalbuminuria as we have found in patients

with essential hypertension³³, as has Pinto Siet-sma³⁴. In his study current smokers had an adjusted relative risk of microalbuminuria of 1.65, former smokers a RR of 1.27, but heavy smokers > 20 cigarettes per day a RR of 1.96.

In Okinawa Tozawa found in a prospective follow up study that the relative risk of developing proteinuria was 1.32 in a prospective follow up study³⁵.

Three population based studies showed an increased risk of chronic kidney disease in smokers. Based on NHANES data 1976 – 1980 Stengel³⁶ found in individuals smoking 1 – 20 cigarettes/day a relative risk of 1.2 and in individuals smoking > 20 cigarettes/day a relative risk of 2.3. This is in line with the observation of Ejerblad³⁷ who found a relative risk of major serum creatinine elevation of 1.51 for smokers > 20 cigarettes/day and a risk of 1.52 for smokers with > 30 pack years. In a large population based study of 23 523 individuals, Haroun³⁸ found that the risk of chronic kidney disease attributable to smoking was no less than 31 %.

It emerges from the above that smoking is a major renal risk factor, the magnitude of which is comparable to that of high blood pressure and proteinuria. It is a modifiable risk factor³⁹ but the attention devoted to this risk factor is far from what it deserves to be.

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