Renal effects of smoking: potential mechanisms and perspectives

Jean-Michel Halimi and Albert Mimran

Department of Medicine and Hypertension, Montpellier University Hospital, Montpellier, France

Introduction

It was recently suggested that smoking, in addition to its well-known cardiovascular consequences, could accelerate the progression of renal diseases [1]. However, our understanding of the acute effects and long-term influence of smoking on renal haemodynamics and albuminuria is poor, and many questions remain unanswered.

Smoking and progression of renal diseases

Increasing evidence suggests that chronic smoking adversely influences the prognosis of nephropathies [1]: smoking increases the risk of microalbuminuria and accelerates the rate of progression from microalbuminuria to proteinuria and subsequent renal failure in type 1 diabetes mellitus [1,2]. The prevalence of micro- and macro-albuminuria was higher in smokers than in non-smokers with type 2 diabetes mellitus in a population-based cohort [3]. Regarding non-diabetic nephropathies, among 270 patients with polycystic kidney disease, proteinuria was more frequent in smokers than non-smokers [4]. In addition, the median time to end-stage renal disease (ESRD) was shorter in smokers than non-smokers (145 vs 273 months) among 160 patients with lupus nephritis [5]. Furthermore, a recent case-control study conducted in patients with polycystic kidney disease and IgA nephropathy indicated that smoking was a risk factor for ESRD in men who did not receive angiotensin-converting enzyme inhibitors [6]. Altogether these findings suggest that smoking is a modifiable factor influencing the renal prognosis of patients with diabetic and non-diabetic renal diseases. However, it is possible that the effects of smoking are modulated by several parameters, including gender, control of arterial pressure and type of anti-hypertensive medications (i.e., angiotensin-converting enzyme inhibitors).

Effects of chronic smoking on renal haemodynamics and urinary albumin excretion in subjects without overt nephropathy

The effects of chronic smoking on renal haemodynamics are not well known in subjects without pre-existing renal disease. Reduced effective renal plasma flow but similar glomerular filtration rate, assessed with $[^{51}\text{Cr}]\text{EDTA}$ clearance, were observed in a recent study comparing 24 apparently normal smokers over 50 years old to 30 non-smokers admitted to an angiology outpatient department [7]. In the absence of a larger study confirming these findings, it must be borne in mind that among 120 insulin-dependent normo-tensive diabetic subjects without renal dysfunction or proteinuria, chronic smokers had on average higher glomerular filtration rates (assessed with isotopic methods) than non-smokers [8]. At present, it is thus unknown whether smoking has a long-term influence on renal function in normal subjects without overt nephropathy.

Smoking was associated with excessive urinary albumin excretion in hypertensive subjects [9]; in fact the prevalence of microalbuminuria was twofold higher in lean, never-treated hypertensive smokers than in non-smokers [9]. Similar results were also reported in normotensive subjects [10]. Of note, the most important determinant of microalbuminuria is usually arterial pressure, especially when ambulatory arterial pressure is used [11]; however, systolic and diastolic arterial pressures were not different between smokers and non-smokers [9].

The relationship between smoking and microalbuminuria may have relevance to renal function outcome [11]. In hypertensive patients, microalbuminuria is probably the consequence of an increased transglomerular passage of albumin in most cases [11], except maybe in those with primary aldosteronism [12]. Although it is not known with certainty whether microalbuminuria is an early indicator of future renal failure development, it is important to note that 54 hypertensive patients with baseline microalbuminuria had a faster decrease in creatinine clearance than 87 normoalbuminuric patients within a follow-up period of 7 years, despite good arterial pressures [13]. Excessive urinary albumin excretion is also a marker of increased cardiovascular risk: 12/54 (21.3%) cardiovascular events occurred in microalbuminuric patients as compared to 2/87 (2.3%) patients with normoalbuminuria in the same study [13].

Acute renal effects of smoking or nicotine

In a recent study, oral administration of a 4-mg nicotine gum was associated with a marked and
proportional decrease in effective renal plasma flow and glomerular filtration rate in non-smokers whereas no change in these parameters was observed in habitual smokers [14]. The absence of an acute effect of smoking on glomerular filtration rate in chronic smokers was also documented in a prospective randomized study including type 1 diabetic subjects [15]. In contrast, in another study, acute smoking or administration of nicotine caused reduced glomerular filtration rate and filtration fraction, but did not change effective renal plasma flow in normal volunteers who were occasional smokers [16]; nevertheless, glomerular filtration rate was unchanged during acute smoking in the seven smokers with IgA nephropathy [16].

Nicotine gum administration or cigarette smoking resulted in no change in urinary albumin excretion in smoker and non-smoker normal volunteers [14] and in habitual smokers with type 1 diabetes mellitus [15]. In contrast, the urinary albumin/creatinine ratio tended to rise in occasional smokers with IgA nephropathy submitted to cigarette smoking whereas urinary albumin excretion remained below the detection threshold in chronic smokers in the study by Ritz et al. [16]. Finally, it appears that the acute effects of smoking on renal haemodynamics and urinary albumin excretion may differ depending on smoking habits and underlying pathology.

**Potential mechanisms**

Since arterial pressure is one of the main determinants of the renal prognosis, it is tempting to relate the influence of smoking on the progression of renal disease to its effects on arterial pressure. Indeed, arterial pressure rises during and after each cigarette smoked, and it has been reported that hypertensive smokers are more likely to develop malignant hypertension than non-smokers. However, epidemiological studies have shown that chronic smokers usually exhibit lower arterial pressure than non-smokers.

Interestingly, it was demonstrated that cigarette smoking (or nicotine) could cause plasma endothelin levels to rise [17]. It was also shown that plasma endothelin levels correlated with effective renal plasma flow in smokers [7]. Since endothelin was implicated in the progression of nephropathies in experimental models and in humans treated with cyclosporin, it is also tempting to speculate that endothelin may mediate some of the renal effects of smoking. Quite evidently, other hormones released following cigarette smoking or nicotine intake, including vasopressin, thromboxane, and ACTH, may also play a role.

It was shown that smoking leads to excessive formation of oxygen-free radicals. The consequence of such repeated oxidative stress may be worsened by the relative deficit in plasma ascorbic acid usually observed in chronic smokers. Endothelial dysfunction related to oxidative stress was demonstrated by abnormal endothelium-dependent vasodilatation of the forearm vasculature in chronic smokers (and also passive smokers) in response to acetylcholine or nitrates [18]; notably, this response was improved by the administration of vitamin C [19]. Whether this endothelial dysfunction has any long-term adverse influence on renal function is presently unknown. Interestingly, we observed that the acute reduction in glomerular filtration rate in non-smokers who received a 4-mg nicotine gum was associated with an even greater decrease in urinary excretion of cyclic guanosine monophosphate (cGMP) (a marker of the interaction between atrial natriuretic peptide/nitric oxide and effector cells); no difference in haemocrit was noted between smokers and non-smokers, and therefore the fall in urinary cGMP could be interpreted as a marker of the impairment in the production of nitric oxide [14].

Cigarette smoking causes a nicotine-induced stimulation of the sympathetic nervous system (i.e. adrenaline and noradrenaline release) that acutely increases arterial pressure and heart rate. The implication of the sympathetic nervous system in the acute renal vasoconstriction observed following nicotine gum administration was unlikely since arterial pressure and heart rate rose in both smokers and non-smokers, whereas glomerular filtration rate and effective renal plasma flow decreased only in non-smokers [14]. Nevertheless, the sympathetic nervous system may play a role in the chronic renal effects of smoking.

**Perspectives**

Nephrologists have been alerted of the renal risks of smoking by the review of Orth et al. [1]. The role of chronic smoking in the progression of renal diseases remains poorly understood, but it has been convincingly demonstrated for type 1 diabetes mellitus (although it is less well documented for type 2 diabetic mellitus, polycystic kidney disease, lupus nephritis, and IgA nephropathy). Although it has not been demonstrated by evidence-based medicine that these findings hold true for all nephropathies, it is clear that all patients with renal disease, whatever its cause, must be asked to stop smoking.

Finally, a deleterious long-term effect of smoking on the age-related decline of renal function has not thus far been documented in normal subjects. Further studies will have to investigate whether smoking plays a prominent role in the development of renal disease, especially renal vascular disease such as nephrosclerosis, a major cause of ESRD in the elderly. Investigations including longitudinal studies with precise assessment of renal haemodynamics in normal subjects and patients with renal diseases are urgently needed.

**References**


