

Smoking and the Kidney

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Nephrologists “rediscovered” smoking as a major renal risk factor in 1997 (1), although investigators in the 19th and 20th centuries had noted an association between smoking and renal damage (2). In the past few years the knowledge about the renal risks of smoking has expanded rapidly. The patients who are at high risk to be affected by the adverse renal effects of smoking have been identified, and earlier observations in the 1970s and 1980s have been confirmed by prospective studies.

Adverse Renal Effects of Smoking in the General Population

Smoking Increases Urinary Albumin/Protein Excretion

It is noteworthy that smoking increases the urinary albumin concentration, even in a range of albumin concentrations below the level of microalbuminuria. This has been well documented in a study including 40,619 subjects aged 28 to 75 yr (3). Even in nondiabetic and nonhypertensive individuals, smoking was independently associated with microalbuminuria (4). A cross-sectional study in 7476 nondiabetic subjects (5) documented that the urinary albumin excretion rate was correlated with the number of cigarettes smoked. After adjustment for potential confounding factors, subjects who smoked <20 cigarettes/d and subjects who smoked >20 cigarettes/d, respectively, showed a dose-dependent association between smoking and high normal urinary albumin concentration (relative risk [RR]: 1.33 and 1.98, respectively) and microalbuminuria (RR: 1.92 and 2.15, respectively). A study of 28,409 subjects (6) found a marked risk of irreversible proteinuria in smokers, including moderate smokers. These results from Europe have recently been confirmed by a preliminary report that also documents an association between smoking and albuminuria in a large cross-sectional probability sample of adults in the United States (7).

Evidence for a Smoking-Induced Decline of Renal Function in the Elderly

There is growing evidence that smoking increases not only the risk of albuminuria/proteinuria but also the risk for renal functional deterioration. In the study of Halimi *et al.* (6), smokers did not exhibit lower creatinine clearance values than

never-smokers. Creatinine clearance was even slightly higher in current smokers, at least in men. This was also true when normotensive and hypertensive subjects were analyzed separately. The difference was, however, small. The effect of current smoking on creatinine clearance was reversible upon discontinuation of smoking. These data are compatible with the notion of early hyperfiltration. Data from the prospective Multiple Risk Factor Intervention Trial (MRFIT) which included 332,544 men, indicate, however, that smoking also increases the risk of renal failure in the general male population (8). In a preliminary communication, a dose-dependent increase of the relative risk of end-stage renal failure (ESRF) was found in smokers as compared with nonsmokers (up to 1.69 for heavy smokers) (9). The increase in risk was independent of confounding factors. Unfortunately, the preliminary data on the relative risk of ESRF conferred by smoking have never been published as a full-size paper.

Additional information is now available from a retrospective case-control study analyzing data obtained in 4142 nondiabetic subjects above age 64 yr who had two measurements of serum creatinine performed at least 3 yr apart (10). The number of cigarettes smoked in this elderly population was highly associated with an increase in serum creatinine >27 $\mu\text{mol/L}$ (>0.3 mg/dl). The definition for renal functional deterioration in this study is undoubtedly weak, but smoking may be one of the factors explaining why an impairment of renal function is observed in some but not all elderly people. This assumption is in line with the observation in a sample of 455 adults in Wadena, Minnesota (11), in whom the decrease in creatinine clearance was greater in ex-smokers and current smokers than in nonsmokers.

It can be concluded (1) that smoking increases the risk of albuminuria/proteinuria in the general population and (2) that there is some evidence to indicate that smoking increases the risk of renal functional impairment in the general population, particularly in men and in the elderly. Large prospective studies investigating hard renal end points are, however, clearly indicated.

Adverse Renal Effects of Smoking in Patients with Primary Hypertension

Smoking Increases Urinary Albumin/Protein Excretion

Proteinuria is found in 4 to 18% and albuminuria in 10 to 25% of patients with primary hypertension. Several studies documented that smoking is an independent predictor of (micro)albuminuria in otherwise healthy hypertensive subjects. The prevalence of microalbuminuria is almost double in smoking than nonsmoking lean patients with primary hypertension

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(12). Furthermore, smoking is the strongest predictor for albuminuria in patients with primary hypertension (13). The Heart Outcome Prevention Evaluation (HOPE) study (14) documented that smoking was an independent determinant of microalbuminuria in all participants, *i.e.*, nondiabetic and diabetic patients with a high cardiovascular risk profile. A recent study (15) found that patients with hypertension and left ventricular hypertrophy smoking >20 cigarettes/d had a 1.6-fold higher prevalence of microalbuminuria and a 3.7-fold higher prevalence of macroalbuminuria than never-smokers.

Evidence for a Smoking-Induced Decline of Renal Function

Important new information has become available concerning the negative impact of smoking on renal functional deterioration in hypertensive patients. Regalado *et al.* (16) performed a prospective study including 51 patients with primary hypertension (mean age, 51.7 ± 2.2 yr) for a mean follow-up of 35.5 mo. Despite reduction of mean arterial BP from 126.8 ± 1.3 mmHg to 96.5 ± 1.1 mmHg, plasma creatinine increased from $133 \pm 9 \mu\text{mol/L}$ (1.5 ± 0.1 mg/dl) to $168 \pm 18 \mu\text{mol/L}$ (1.9 ± 0.2 mg/dl). Factors that independently predicted renal functional decline were smoking, higher initial plasma creatinine level, and black ethnicity. Smoking was by far the most powerful predictor of renal functional deterioration. The mean increase in plasma creatinine was greater than what can be expected in a representative sample of patients with primary hypertension. It is therefore uncertain whether the data of this well performed, but small prospective study can be generalized. It is of note that a large prospective US study (17) that included 5730 black and 6182 non-black hypertensive male subjects of similar age (mean age 52.5 ± 10.2 yr) did not find a relation between smoking and the risk of ESRF during a minimum of 13.9 yr of follow-up.

Thus, the issue of whether smoking increases the rate of progression in patients with primary hypertension remains controversial. Considering the proven effects of smoking on albuminuria/proteinuria, it is a justifiable conclusion that smoking should be considered as a renal risk factor in hypertensive patients.

Adverse Renal Effects of Smoking in Patients with Renal Disease

The literature available indicates that patients with renal disease are a high-risk group particularly susceptible to smoking-induced renal damage.

Diabetic Nephropathy. The first reports that documented an increased renal risk in smokers were retrospective studies in patients with type 1 diabetes. In 1978, Christiansen (18) provided evidence that smokers have a higher risk to develop diabetic nephropathy than nonsmokers. This observation was confirmed by Telmer *et al.* (19) in a larger series that included 668 patients with type 1 diabetes. The frequency of nephropathy was progressively higher with increasing cigarette consumption. Diabetic nephropathy was present in 13% of patients who smoked <10 cigarettes/d but in >25% in patients who

smoked 30 cigarettes/d. Subsequently, numerous studies confirmed the increased renal risk in smokers with type 1 and type 2 diabetes mellitus.

The available literature documents that smoking (1) increases the risk to develop microalbuminuria (14,20–30), (2) accelerates the rate of progression from microalbuminuria to manifest proteinuria (31–36), and (3) accelerates progression of renal failure (32,37–40).

The negative impact of smoking on the kidney in patients with diabetes mellitus is independent of the age of the patient and of the duration of the disease. An association between albuminuria/proteinuria and smoking has been found among both adolescents with type 1 diabetes (25) and patients with type 1 diabetes who survived >30 to 40 yr (41,42).

What is the magnitude of the adverse renal effects of smoking in patients with diabetes mellitus? Chase *et al.* (20) reported that in a group of 359 young subjects with type 1 diabetes the prevalence of borderline (>7.6 $\mu\text{g}/\text{min}$) and frankly elevated (>30 $\mu\text{g}/\text{min}$) urinary albumin excretion rate was 2.8-fold higher in smokers than nonsmokers. Similarly, the risk of microalbuminuria in the first months after the diagnosis of type 2 diabetes is highly increased in current smokers; in a study including 85 consecutive patients with newly diagnosed type 2 diabetes, the odds ratio for the presence of microalbuminuria was 26.3 for current smokers compared with only 3.42 for a 1% increment in glycosylated HbA_{1c} (29). Although the confidence intervals were wide, the data indicate the importance of smoking compared with glycemic control as a classic renal risk factor in diabetes mellitus.

Concerning the risk to progress from microalbuminuria to overt proteinuria (>300 mg/d), a prospective study with an observation time of 4 yr included 794 patients with type 2 diabetes and reported a 2- to 2.5-fold higher relative risk in heavy smokers than in never-smokers (35).

Patients with diabetes mellitus are the fastest growing population reaching ESRF; therefore, the impact of smoking on the rate of progression is of particular importance. Sawicki *et al.* (38) calculated the adjusted odds ratio for progression of nephropathy in patients with type 1 diabetes. Progression was defined as an increase in proteinuria >20% and/or a reduction of GFR >20% after 1 yr of follow-up. The odds ratio was 2.74 for every 10 cigarette pack-years ([mean number of cigarettes smoked per day/20] \times number of smoking years). In this prospective study with a follow-up of 1 yr, all 93 patients had been on intensified insulin and effective antihypertensive therapy; confounding effects of hyperglycemia and hypertension were therefore minimized. Another prospective study investigated the progression rate in the predialysis phase. Sixteen patients with type 1 diabetes and 16 patients with type 2 diabetes were studied (37). At study-entry, all patients had near-normal renal function and overt proteinuria. Besides mean systolic and diastolic BP, smoking ≥ 10 cigarettes/d was the only independent variable associated with the rate of decrease of creatinine clearance. In patients with type 1 diabetes, the rate of decline in creatinine clearance was 1.24 ± 0.29 ml/min per mo in smokers and 0.86 ± 0.31 ml/min per mo in nonsmokers. In patients with type 2 diabetes, the rate of decline in creatinine

clearance was 1.21 ± 0.34 ml/min per mo in smokers and 0.73 ± 0.38 ml/min per mo in nonsmokers. Thus, the impact of smoking on the rate of progression is similar in type 1 and type 2 diabetes. The rate of decline in GFR is approximately 55% higher in smokers compared with nonsmokers. These data are of great interest, but it has to be pointed out that they have been collected on the basis of a limited sample size and that BP had not been well controlled.

A recent prospective study by Chuahirun and Wesson (43) provides further information concerning the impact of smoking on renal functional deterioration in patients with type 2 diabetes. BP was well controlled according to current standards (mean arterial BP, 92 ± 1 mmHg), including an angiotensin-converting enzyme (ACE) inhibitor among the antihypertensive drugs. Glycemic control was also acceptable with a mean HbA_{1c} during follow-up of $7.5 \pm 0.4\%$. The 33 patients with type 2 diabetes and manifest nephropathy were followed for 5.3 yr. The initial serum creatinine was 93 ± 7 μ mol/L (1.05 ± 0.08 mg/dl) in smokers ($n = 13$) and 95 ± 3 μ mol/L (1.08 ± 0.03 mg/dl) in non-smokers ($n = 20$). At the end of observation time, the increase of serum creatinine was more pronounced in smokers as compared with nonsmokers, *i.e.*, 157 ± 18 μ mol/L (1.78 ± 0.2 mg/dl) *versus* 117 ± 4 μ mol/L (1.32 ± 0.04 mg/dl). This difference was not explained by potential confounding factors, and regression analysis revealed that smoking was the only parameter that significantly predicted the renal functional decline. Thus, smoking seems to remain a renal risk factor despite lowering of BP to the target level using currently recommended therapy, at least in patients with type 2 diabetes. The intriguing finding that the nephroprotective effect of ACE inhibitor treatment is abrogated, at least partially, in patients with type 2 diabetes who smoke must be confirmed in a larger prospective study. At least in a retrospective study in patients with diabetes mellitus, smoking did not confer an increased renal risk when BP was adequately controlled, including an ACE inhibitor (Orth SR, unpublished data). This preliminary finding parallels our previous observation in a retrospective case-control study on patients with primary renal disease in which we found that ACE inhibition protects against smoking-induced renal functional decline (44), possibly as a result of improved endothelial function after ACE inhibition (45). *In vitro* data suggest that the beneficial effect of ACE inhibitors is partly mediated by scavenging free radicals and by attenuation of the cigarette-induced suppression of nitric oxide production (46), but other possibilities are not excluded.

In summary, there is clear evidence that smoking has adverse effects on the onset and evolution of diabetic nephropathy in type 1 and type 2 diabetes mellitus. In my opinion, further studies are needed to assess the extent to which smoking counteracts the nephroprotective effect of ACE inhibitor treatment in these patients.

Nondiabetic Renal Disease. There is no pertinent evidence in the literature that the risk of developing glomerulonephritis or systemic disease with renal involvement is higher in smokers (47–50). Solid evidence has accumulated, however, that smoking is a major renal risk factor in patients with established primary renal disease.

Primary Renal Disease. An adverse effect of smoking on renal outcome was first suggested by a study in patients with autosomal dominant polycystic kidney disease (ADPKD) in which smoking was a risk factor for the presence of proteinuria (51). We performed a retrospective matched case-control study to assess whether smoking increases the risk to progress to ESRF in patients with IgA glomerulonephritis or ADPKD (44). Analysis of smoking (quantitated in pack-years) showed no strata inhomogeneity between renal diseases; IgA glomerulonephritis and ADPKD were therefore pooled for statistical analyses. Small sample size and modest average tobacco consumption caused the subgroup of women to be excluded from further analyses. Table 1 shows the distribution of cigarette smoking in male patients. The crude estimators for different quantitative levels of smoking document a dose-dependent increase in the risk for ESRF in male smokers compared with nonsmokers or moderate smokers (0 to 5 pack-years). After adjustment for possible confounders, multivariate analysis revealed that the risk for ESRF was substantially higher in male smokers with no history of ACE inhibitor treatment. In contrast, the risk for smokers with a history of ACE inhibitor treatment was not significantly increased (Table 2). Another case-control study confirmed that male patients with glomerulonephritis who smoke are at increased risk of renal function impairment (52). In this study, the negative impact of smoking was particularly marked in elderly hypertensive males.

The design of these studies was retrospective, and a prospective study would obviously be desirable. At least some prospective information is available. Samuelsson and Attman (53) performed a *post hoc* analysis of a prospective study that had originally been designed to evaluate the role of dyslipidemia on the progression of renal failure. The study comprised 73

Table 1. Epidemiologic evidence for the adverse renal effects of smoking

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- Dose-dependent increase of urinary albumin excretion rate/proteinuria in cigarette smokers of the general population.
 - Dose-dependent increase of the risk of end-stage renal failure (ESRF) in male cigarette smokers of the general population.
 - Independent predictor of (micro)albuminuria in patients with primary hypertension.
 - Most powerful predictor of renal functional decline in patients with primary hypertension.
 - Increased risk for progression of renal failure in patients with primary renal disease.
 - In type 1 and type 2 diabetes mellitus: independent risk factor for the onset of microalbuminuria, for progression of microalbuminuria to manifest proteinuria, and for acceleration of the rate of progression of diabetic nephropathy to ESRF.
 - Increased risk for atherosclerotic renal artery stenosis/ischemic nephropathy.
 - Increased risk for deterioration of renal allograft function.
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Table 2. Crude smoking-associated risk of terminal renal failure in 144 male patients with IgA glomerulonephritis or autosomal dominant polycystic kidney disease (44)

Pack-Years	Cases (n [%])	Controls (n [%])	OR	95% CI	<i>P</i> ^a
0 to 5	26 [36]	47 [65]	1.0		
5 to 15	17 [24]	11 [15]	3.5	1.3 to 9.6	0.017
>15	29 [40]	14 [19]	5.8	2.0 to 17	0.001

^a Wald χ^2 .**Table 3.** Smoking-associated risk of terminal renal failure (stratified for angiotensin-converting enzyme [ACE] inhibitor treatment and adjusted for systolic BP) in 144 male patients with IgA glomerulonephritis or autosomal dominant polycystic kidney disease (44)

Pack-Years	ACE Inhibitor			No ACE Inhibitor		
	OR	95% CI	<i>P</i> ^a	OR	95% CI	<i>P</i> ^a
<5	1.0			1.0		
>5	1.4	0.3 to 7.1	0.65	10.1	2.3 to 45	0.002

^a Wald χ^2 .

patients with primary renal disease. The authors report that smoking status at entry was related to the decline in GFR after 3.2 yr of follow-up; in patients with chronic glomerulonephritis, the loss of GFR was 5.3 ml/min per yr in heavy smokers but only 2.5 ml/min per yr in nonsmokers. Thus, smoking appears to double the rate of progression in patients with chronic glomerulonephritis. This finding is in agreement with what had been found in patients with diabetes mellitus (37). Nevertheless, the data of Samuelsson and Attman (53) have to be interpreted with caution, because statistical significance was not reached, possibly because of the short observation time and the small number of patients investigated.

The fact that we (44) and Stengel *et al.* (52) did not find an adverse effect of smoking on renal function in the small female subgroup is presumably related to the limited sensitivity of the studies. Certainly the data do not permit to rule out an adverse effect of smoking on renal prognosis in women, but we cannot exclude that—at least before menopause—women are less affected by the adverse renal effect of smoking. In favor of this hypothesis would be the finding in one study on 246 patients with type 1 diabetes (54) in which no relation was found between smoking and diabetic nephropathy among the female patients (*n* = 106) in contrast to the male patients.

Systemic Diseases Involving the Kidney. Only limited information is available concerning the effect of smoking on renal function in systemic diseases with renal involvement. A retrospective cohort study on 160 patients with a median follow-up of 6.4 yr documented that smoking at the time of onset of lupus nephritis was an independent risk factor for more rapid progression to ESRF (55). Life-table analysis was performed to calculate the median time interval to ESRF. It was 145 mo in smokers and in excess of 273 mo in nonsmokers. This observation seems to be solid, because the effect of smoking was

Table 4. Potential pathomechanisms of smoking-induced renal injury

- Increased sympathetic nerve activity.
- Increase in BP and heart rate.
- Decreased fall in nighttime BP.
- Increase in renal vascular resistance leading to a decrease in GFR and renal plasma flow.
- Increase in intraglomerular capillary pressure.
- Aggravation of hyperfiltration in patients with diabetic nephropathy.
- Atherosclerosis of renal arteries and myointimal hyperplasia of the intrarenal arteries and arterioles.
- Endothelin-1–mediated and/or angiotensin II–mediated proliferation and matrix accumulation of vascular smooth muscle cells, endothelial cells, and mesangial cells.
- Tubulotoxic effects with alteration of tubular function.
- Toxic effects on endothelial cells.
 - alteration of the prostaglandin/thromboxane metabolism.
 - oxidative stress through generation of reactive oxygen species.
 - NO depletion.
 - impairment of endothelial cell-dependent vascular dilation.
 - increased adhesion of monocytes to the endothelium.
 - carbon monoxide–induced hypoxia.
- Increased clotting of platelets.
- Impaired lipoprotein and glycosaminoglycan metabolism.
- Modulation of the immune response.
- Vasopressin-mediated antidiuresis.
- Insulin resistance.

independent of hypertension and immunosuppressive treatment. These data were not confirmed, however, by a recent prospective study including 70 consecutive patients with lupus nephritis who were compared with 70 age- and sex-matched controls with systemic lupus erythematosus without evidence of nephropathy (56). After 10 yr of follow-up, 67% of lupus nephritis patients had normal plasma creatinine, 24% had renal failure, and 9% ESRF. Hyperlipidemia and hypertension at study onset were the only factors associated with development of renal failure. No other studies have investigated this issue; therefore, the influence of smoking on prognosis of lupus nephritis remains unclear.

The hypothesis that heavy smoking might be a risk factor for the development and/or progression of pauci-immune ANCA-positive extracapillary glomerulonephritis has been forwarded (57) but without supporting data. Nevertheless, it is conceivable that smoking-induced endothelial cell damage may predispose to the formation of antibodies against nuclear cell antigens extruded from endothelial cells or endothelial cell adherent polynuclear cells. Studies of this interesting and clinically relevant topic are needed. It should be mentioned in passing that in patients with anti-glomerular basement membrane glomerulonephritis smoking strikingly increases the risk of pulmonary hemorrhage (Goodpasture syndrome) (1).

Smoking and Atherosclerotic Renal Artery Stenosis/Ischemic Nephropathy

The prevalence of atherosclerotic renal artery stenosis is increasing in the aging population, and ischemic nephropathy is a significant cause of ESRF in patients over 65 yr of age (58). The prevalence of renal vascular stenosis is higher in patients with peripheral vascular disease (59). The latter is common in smokers; it is not therefore surprising that smokers have a higher risk of critical atherosclerotic renal artery stenosis (60,61). As one would expect, a high proportion of patients with unilateral (62) or bilateral (63) atherosclerotic renal artery stenosis are smokers.

No reports are available in patients with renal artery stenosis/ischemic nephropathy comparing the rate of progression of renal failure in smokers and nonsmokers, but it is likely that smoking accelerates the course of renal failure. This assumption is based on the consideration that apart from luminal narrowing of the renal artery, a combination of arteriolar and atheroembolic damage (*i.e.*, cholesterol microembolism) is thought to contribute to progressive loss of renal function. Actually, smoking is a known risk factor for cholesterol microembolism (64).

In a group of 89 normotensive, nondiabetic elderly subjects with different degrees of peripheral atherosclerosis and no clinical signs of ischemic nephropathy, renovascular hypertension, or other nephropathies, evaluation of renal function and renal plasma flow revealed that, despite normal values for GFR, renal plasma flow declined progressively in parallel with the severity of peripheral atherosclerosis (65). Stepwise multiple regression showed that the decrease in renal plasma flow was best explained by smoking and serum LDL cholesterol.

There was a close association between the severity of extrarenal atherosclerosis and renal hypoperfusion; the authors therefore concluded that this was the result of beginning ischemic nephropathy. Renal function should obviously be assessed in patients with extrarenal atherosclerosis, particularly in those with classic cardiovascular risk factors including smoking.

Adverse Effects of Smoking in Patients with a Renal Transplant

It has been contrainтуitively reported that smoking does not appear to increase the risk of microalbuminuria in patients with a renal transplant (66). The first studies published indeed indicated a lack of correlation between smoking and the development of progressive allograft dysfunction (67). Recent prospective data do, however, provide solid evidence for an adverse effect of smoking on graft function.

A cohort study of 645 adult renal allograft recipients was performed from 1985 to 1995 to evaluate the relationship between smoking and graft outcome (68). Twenty-four percent of recipients (156 of 645) were smokers at the time of transplant evaluation. Of these, 90% continued to smoke after transplantation. Pretransplant smoking was significantly associated with reduced overall graft and death-censored graft survival. Patients who were smokers at the time of pretransplant evaluation had kidney graft survival of 84%, 65%, and 48% at 1, 5, and 10 yr, respectively, compared with nonsmoker graft survival of 88%, 78%, and 62% ($P = 0.007$). Pretransplant smoking adversely affected death-censored graft survival in recipients of cadaveric and of living donor kidneys. Reduced graft survival in pretransplant smokers could not be accounted for by differences in rejection episodes (64% *versus* 61%). In a multivariate analysis, pretransplant smoking was associated with a relative risk of 2.3 for graft loss. Among patients with a smoking history before transplantation, death-censored graft survival was significantly higher for those who quit smoking before transplant evaluation. Thus, this study documents that cigarette smoking before kidney transplantation contributes significantly to allograft loss, an effect that is not explained by increases in rejection episodes or patient death. The finding that smoking cessation before renal transplantation has beneficial effects on graft survival is of major importance for the management of patients with ESRF who are considered for renal transplantation. In a retrospective analysis, current smoking has also been documented to be a risk factor for decreased graft survival in first-time kidney transplant recipients aged ≥ 60 yr (69).

The effect of smoking on renal allograft function may depend on the renal disease that has led to ESRF. In patients who had reached ESRF as a result of lupus nephritis, the risk of renal transplant loss was substantially higher in smokers (70). In this study, smoking was associated with the highest relative risk for allograft loss (RR, 2.5; $P < 0.0001$), higher than other factors such as delayed graft function, acute rejection episodes, and total HLA mismatches. Lupus nephritis accounts only for a small proportion of patients requiring renal transplants, but the results may be of major clinical importance. It is possible

that the alterations of the immune response reported in smokers (1) are particularly detrimental in patients with immunoregulatory abnormalities such as systemic lupus erythematosus.

It would also be conceivable that smoking among kidney donors imperils the allograft outcome, but one study on kidney donor lifestyle factors, including smoking, drinking, drug use, and sexual history, found no significant adverse effect on renal allograft survival (71).

Pathohistologic Features of Smoking-Induced Renal Damage

In a renal biopsy study, the histologic findings of 107 patients with chronic renal failure were assessed to investigate the effect of smoking on glomerulosclerosis and vascular damage (72). Most of these patients suffered from glomerular disease with marked proteinuria, only a minority had been treated with an ACE inhibitor at the time of biopsy, and BP was not well controlled (mean BP, 152/91 mmHg). Smoking was not associated with the severity of glomerulosclerosis. Compared with nonsmokers, ever-smokers exhibited more severe myointimal hyperplasia. This finding was particularly evident in patients >50 yr of age. In younger patients, a trend toward arteriolar changes was evident in smokers, but this finding did not reach statistical significance. In women, no correlation was observed. This may be due to the fact that women were less likely to be smokers and smoked less than half as many pack-years than did men.

The above study is important, because it documents that smoking has an adverse effect on the morphology of intrarenal arterioles, at least in elderly male patients with renal disease. Hypertension *per se* does not seem to be related to myointimal hyperplasia of intrarenal arterioles (73). Against this background, the effect of smoking is relevant. The negative finding concerning the severity of glomerulosclerosis does of course not exclude an effect of smoking on glomerular structure.

Using a more precise method for quantification of renal damage, our group found more severe glomerulosclerosis and tubulointerstitial fibrosis in the subtotally nephrectomized rat treated with a cigarette smoke extract dissolved in acetone (74). Whether this is also true for humans with noninflammatory renal disease remains to be determined. An increase in glomerular basement width in patients with type 2 diabetes who smoke has been reported in a preliminary biopsy study (75).

Potential Mechanisms of Smoking-Induced Renal Damage

Several potential mechanisms of smoking-induced renal damage have been discussed (76), but the precise nature of the nephrotoxic effect of smoking is not well understood. The postulated smoking-induced pathomechanisms causing renal damage are summarized in Table 2. These include acute effects, particularly sympathetic activation (influencing BP and renal hemodynamics), and chronic effects, particularly endothelial cell dysfunction (diminished nitric oxide availability, diminished endothelial cell-dependent vasodilation, and intimal cell hyperplasia).

The nicotine-induced increase in BP and heart rate via sympathetic activation and vasopressin release appears to be a major mechanism contributing to the adverse renal effects of smoking (for review see (76)). Nicotine directly stimulates catecholamine release from peripheral sympathetic nerve endings and the adrenal medulla. Increased sympathetic activity *per se* accelerates progression of renal failure independent of BP effects (77).

In view of the importance of BP on the evolution of renal disease, the effects of smoking on BP are of interest. Ambulatory BP measurements documented that, parallel with the stimulation of the sympathetic system, smoking causes a significant, but transient (approximately 30 min) increase of BP. This has been shown in healthy subjects, in hypertensive subjects, in patients with type 1 and type 2 diabetes, and in patients with primary renal disease (for review see reference 67).

Smoking also seems to alter the diurnal rhythm of BP. Hansen *et al.* (78) reported that the night/day ratio of systolic and diastolic BP in healthy smokers was lower than in nonsmokers. A preliminary communication (79) documented a decreased ratio of daytime to nighttime BP in both smoking healthy volunteers and in subjects with type 1 diabetes. In patients with diabetes mellitus, presence or absence of autonomic neuropathy is a major determinant of the effects of smoking on BP. For instance, among patients with type 1 diabetes, smoking increased systolic BP only in subjects without autonomic neuropathy (80).

Smoking causes alterations of intrarenal hemodynamics, particularly a decrease in renal plasma flow as a result of renal vasoconstriction (for review see reference 67). Vasoconstriction is abrogated by pretreatment with the β -blocker atenolol (81). This finding together with the observation of an abrogation of the adverse effect of smoking by ACE inhibitor treatment in patients with primary renal disease (44) is consistent with the hypothesis depicted in Figure 1.

There is no doubt that further long-term effects of smoking contribute to its nephrotoxic effect, particularly endothelial cell damage and oxidative stress. A genetic approach to explain the different susceptibility of individuals to smoking-induced organ damage has been proposed by Wang *et al.* (82): the risk of atherogenesis appears to be excessively high in patients who are homozygous for the endothelial nitric oxide synthase 4a (ecNOS4a) gene. This genotype predisposes to endothelial dysfunction and is associated with an increased coronary risk in smokers. Whether a similar genetic susceptibility determines an increased renal risk in smokers is an issue that deserves further investigation. In this context, a result of the BERGAMO Nephrologic Diabetes Complications Trial (BENEDICT) is noteworthy: A genetic predisposition of smokers to develop albuminuria was found in carriers of the DD-genotype of the ACE gene (83).

Reversibility of Smoking-Induced Renal Damage

What is the renal benefit derived from smoking cessation? In patients with type 1 diabetes and nephropathy with adequate

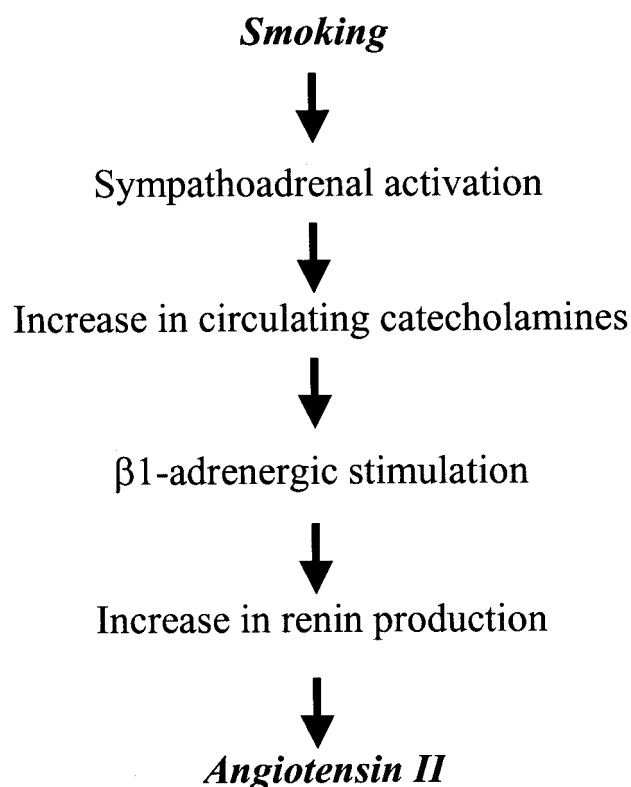


Figure 1. Hypothetical sequence of smoking-induced activation of the renin-angiotensin system as one major pathomechanism of smoking-induced renal damage.

control of BP, cessation of smoking significantly decreased urinary albumin excretion, although glycemia was not perfectly controlled (20). In another study, progression of renal failure was found in 53% of current smokers, but only 33% of ex-smokers and 11% of nonsmokers (38). It is plausible to assume that this is also true in nondiabetic renal disease. In nondiabetic subjects with apparently normal kidneys, Pinto-Sietsma *et al.* (5) found that the risk of microalbuminuria is only minor in ex-smokers, but significant in current smokers. There is some evidence, however, that the smoking-induced decrease in renal plasma flow is not completely reversible after smoking cessation (84).

The present data do not allow for the drawing of a definite conclusion about the magnitude of the renal benefit derived from smoking cessation. When the above data and 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—quite apart from its undoubtedly beneficial effect on cardiovascular risk (67,85).

Conclusion

Smoking is one of the most important remediable renal risk factors. It has a negative impact on renal function even in subjects without apparent renal disease, but the adverse renal

effects of smoking are particularly marked in patients with different types of kidney disease.

Major efforts are justified to help patients quit smoking. These include the most effective pharmaceutical smoking cessation approaches known to date, *i.e.*, therapy with sustained-release bupropion and nicotine replacement therapy (86). Additional psychologic support/counseling therapy is of major importance to further improve the smoking cessation success rate, which is still disappointingly limited.

Management of the renal patient requires information about (1) the magnitude of the renal and cardiovascular risk related to smoking, including the benefits from smoking cessation, and (2) application of the above modern therapeutic modalities in patients willing to stop smoking. To the best of my knowledge, there is no information about the exact pharmacokinetics of sustained-release bupropion in patients with impaired renal function. Apparently, bupropion does not accumulate in renal failure. In contrast, nicotine accumulates in renal failure (87), a fact that has to be considered when treating patients with nicotine replacement therapy. It has to be acknowledged that to date controlled information on the success of a modern smoking cessation strategy in renal patients is not available.

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