Abstract. In recent years, it has become apparent that smoking has a negative impact on renal function, being one of the most important remediable renal risk factors. It has been shown clearly that the risk for high-normal urinary albumin excretion and microalbuminuria is increased in smoking compared with nonsmoking subjects of the general population. Data from the Multiple Risk Factor Intervention Trial indicate that at least in men, smoking increases the risk to reach end-stage renal failure. Smoking is particularly “nephrotoxic” in older subjects, subjects with essential hypertension, and patients with preexisting renal disease. Of interest, the magnitude of the adverse renal effect of smoking seems to be independent of the underlying renal disease. Death-censored renal graft survival is decreased in smokers, indicating that smoking also damages the renal transplant. Cessation of smoking has been shown to reduce the rate of progression of renal failure both in patients with renal disease and in patients with a renal transplant. The mechanisms of smoking-induced renal damage are only partly understood and comprise acute hemodynamic (e.g., increase in BP and presumably intraglomerular pressure) and chronic effects (e.g., endothelial cell dysfunction). Renal failure per se leads to an increased cardiovascular risk. The latter is further aggravated by smoking. Particularly, survival of smokers with diabetes on hemodialysis is abnormal.

Smoking has profound effects on systemic and intrarenal hemodynamics. A smoking-induced increase in BP and heart rate had first been reported in 1907 by Hesse (1). Although others had even found an association between smoking and renal damage (2), this has only been confirmed in 1979 in patients with type 1 diabetes (3), and it was not until 1997 (4) that nephrologists became aware of smoking being a major renal risk factor.

The effects of smoking on BP were a matter of debate in the 1980s. Large epidemiologic studies had found that smokers are not more frequently hypertensive than nonsmokers (5). These studies, however, did not perform ambulatory BP measurement, which besides that smokers weigh less than their more obese nonsmoking counterparts explains these false-negative results (6). More recent studies using ambulatory BP measurement clearly document that smokers have higher BP than nonsmokers, i.e., an increase of approximately 3 to 12 mmHg in mean arterial pressure (MAP). This has been shown in several studies including healthy subjects, hypertensive subjects, patients with type 1 and type 2 diabetes, and patients with primary renal disease (for review, see reference 7). With an increase of 12 mmHg in MAP, patients with renal disease seem to be particularly prone to the effect of smoking on BP. There is some evidence, at least in hypertensive patients, that elderly subjects (>50 to 60 yr of age) are more affected than younger subjects (8,9). A recent population-based cross-sectional study investigated 12,417 men who were screened for a routine check-up in France (9). The prevalence and the relative risk of hypertension associated with smoking status were analyzed. Overall, the prevalence of hypertension was higher in former smokers than in never smokers (13.5 versus 8.8%; P < 0.001). The risk of hypertension was higher (odds ratio [OR], 1.31 [1.13 to 1.52]; P < 0.001) in former smokers than in never smokers, independent of age and alcohol intake. Both current and former smokers were at risk for systolic hypertension, especially men aged ≥60 yr. The risk of hypertension was associated with the number of cigarettes smoked daily (OR per 10 cigarettes, 1.13 [1.05 to 1.21]; P < 0.001) and the duration of smoking cessation (OR, 0.99 [0.98 to 1.00]; P = 0.01).

When body mass index was entered into the model, the risk of hypertension in former smokers was no longer significant; current smokers remained at risk for systolic hypertension, however. Some studies found an increase of BP only during daytime, which supports the observation that the effect of smoking on BP is short (lasting approximately 30 min) (7).

The increase in BP (and heart rate) is mediated via direct stimulation of postganglionic sympathetic nerve endings, leading to an increase of plasma concentrations of norepinephrine and epinephrine (10). This effect is related to nicotine per se, because it is not observed when nicotine-free cigarettes are smoked (7).

Concerning intrarenal hemodynamics, Halimi et al. (11) found that the chewing of a nicotine-containing gum leads to a decrease of GFR and effective renal plasma flow in nonsmokers (by 15 ± 4 and 14 ± 4%, respectively) but not in smokers. In smokers, GFR even increased slightly, although this was not significant. These findings could be explained by a much more prominent nicotine-induced increase of renal vascular resis-
tance in subjects who are not used to nicotine exposure, *i.e.* nonsmokers, compared with those used to nicotine exposure, *i.e.* smokers. Thus, in smokers, the response of the kidney to increased systemic BP may be impaired, leading to an increase of GFR and possibly also intraglomerular capillary pressure. This seems to be particularly true for patients with a diseased kidney (12,13). The increase in renal vascular resistance can be inhibited by pretreatment with a \( \beta_1 \)-receptor antagonist (14), which has led to the hypothesis that smoking leads to \( \beta_1 \)-receptor–mediated renin and angiotensin II production (15). The effects of smoking on systemic and intrarenal hemodynamics described above, besides other potential nonhemodynamic pathomechanisms of smoking-induced renal damage (for review, see reference 6), do have severe consequences for the kidney.

**Epidemiologic Evidence for Smoking-Induced Renal Functional Impairment**

**Evidence from Studies in the General Population**

Smoking increases the urinary albumin concentration even in the range defined as normal. This has been well documented in a study that included 40,619 subjects aged 28 to 75 yr (16). Even in nondiabetic and nonhypertensive individuals, smoking was independently associated with microalbuminuria (17). A cross-sectional study in 7476 nondiabetic subjects (18) 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, 1.33 and 1.98, respectively) and microalbuminuria (relative risk, 1.92 and 2.15, respectively). A study in 28,409 subjects (19) found a marked risk of irreversible proteinuria in smokers that was noted even in 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 (20). Recent data from Australia showed that at least as far as proteinuria is concerned, the smoking-related increment in protein excretion is particularly marked in patients with high normal but not frankly elevated systolic BP and post-load glucose concentrations (21). This observation is of particular concern because interaction between and mutual reinforcement of these cardiovascular risk factors is unwelcome indeed. It is interesting that in the study of Briganti *et al.* (21), the risk of renal impairment associated with smoking was restricted to men in whom the OR was impressively increased (OR, 3.59), whereas there was no increased risk at all in women. This is in agreement with a study from Japan (22) and previous studies in patients with primary renal disease (23,24) and diabetic nephropathy (type 1 diabetes) (25), which also failed to show an increased risk in women. Although further studies are needed to get definite answers in this regard (particularly because the number of women enrolled in most of the latter studies was limited, which is particularly critical, because women smoke less than men), the above studies implicate that cigarette smoking confers a higher renal risk in men than in women (26). Whether this is also true for women after menopause, remains to be determined. Furthermore, it has never been investigated whether smoking leads to albuminuria/proteinuria via damaging the glomerular filter or the tubular albumin degradation pathway (27), or both. Damage to the tubular albumin degradation pathway, which is mainly located in proximal tubular cells, would be plausible against the background of proximal tubular damage observed in smokers with presumably healthy kidneys (for review, see reference 7).

The increase of urinary albumin/protein concentration is strong evidence for smoking-induced renal damage and may lead to progressive renal functional deterioration. In the study of Halimi *et al.* (19), smokers did not exhibit lower creatinine clearance values than never smokers. Creatinine clearance was even slightly higher in current smokers than in former smokers and never smokers (100.6 \( \pm \) 13.6 *versus* 98.8 \( \pm \) 13.9 ml/min per 1.73 m\(^2\) \( P < 0.0001 \)) and *versus* 98.5 \( \pm \) 14.0 ml/min per 1.73 m\(^2\) \( P < 0.0001 \)), respectively). This difference was predominant in men and weak in women and was associated with the number of cigarettes smoked daily. It persisted when normotensive and hypertensive subjects were analyzed separately. The effect of current smoking on creatinine clearance was reversible on discontinuation of smoking. These data are compatible with the notion of early hyperfiltration. Data from the prospective Multiple Risk Factor Intervention Trial in 332,544 men indicate, however, that smoking also increases the risk of renal failure in the general male population. 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) (28). The increase in risk was independent of confounding factors.

Additional information is available from a retrospective case-control study that analyzed data obtained in 4142 nondiabetic elderly subjects >64 yr of age, who had two measurements of serum-creatinine performed at least 3 yr apart (29). In this elderly population, the number of cigarettes smoked was highly associated with an increase in serum-creatinine >27 \( \mu \)mol/L. 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. This assumption is in line with the observation in a sample of 455 adults in Wadena, Minnesota (30), in whom the decrease in creatinine clearance was greater in ex-smokers and current smokers than in nonsmokers.

These apparently modest reductions of renal function in the general population are a matter of major concern. Obviously, reduced GFR and albuminuria/proteinuria may increase the risk of ESRF. From a public health perspective, it is even more important that such minor renal dysfunction has dramatic repercussions on the cardiovascular risk. It has recently been documented that a GFR of <60 ml/min and a minor increase of albumin excretion, *i.e.* microalbuminuria, increases the cardiovascular risk by a factor 2 to 3 (31–33).
Evidence from Studies in Patients with Primary Hypertension

The prevalence of microalbuminuria is almost double in smoking than in nonsmoking lean patients with primary hypertension (34). Smoking is the strongest independent predictor of albuminuria in patients with primary hypertension (35). The Heart Outcomes Prevention Evaluation Study (36) 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 (37) found that patients who had hypertension and left ventricular hypertrophy and smoked >20 cigarettes/day had a 1.6-fold higher prevalence of microalbuminuria and a 3.7-fold higher prevalence of macroalbuminuria than never-smokers.

There is only little information about the negative impact of smoking on renal functional deterioration in hypertensive patients. Regalado et al. (38) performed a prospective study in 51 patients with primary hypertension (mean age, 51.7 ± 2.2 yr) for a mean follow-up of 35.5 mo. Despite reduction of MAP from 126.8 ± 1.3 mmHg to 96.5 ± 1.1 mmHg, plasma-creatinine increased from 133 ± 9 μmol/L to 168 ± 18 μmol/L. 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. In this context, it is of note that a large prospective study (39), also from the United States, in 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 of renal failure 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.

Evidence from Studies in Patients with Type 1 and Type 2 Diabetes

Christiansen (3) provided the first evidence that patients who have type 1 diabetes and smoke have a higher risk to develop diabetic nephropathy. This observation was confirmed by several retrospective and some prospective studies (for review, see reference 15). The available literature documents that smoking (1) increases the risk to develop microalbuminuria, (2) accelerates the rate of progression from microalbuminuria to manifest proteinuria, and (3) accelerates progression of renal failure. In this context, the type of diabetes does not play a role. Importantly, the negative impact of smoking on the kidney in patients with diabetes 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 (40) and patients with type 1 diabetes who survived >30 to 40 yr (41,42). An association of smoking and microalbuminuria has also been reported in blacks with newly diagnosed type 1 or type 2 diabetes (43). In a recent prospective study, Chuahirun et al. (44) investigated whether smoking and increased urinary albumin excretion are interrelated predictors of nephropathy progression in 84 patients with type 2 diabetes (mean follow-up, 63.9 ± 0.6 mo). Despite angiotensin-converting enzyme (ACE) inhibition and reduction of MAP from 113.7 ± 1.8 to 92.3 ± 0.6 mmHg (P < 0.001), plasma-creatinine increased (91.1 ± 1.8 to 110.5 ± 3.5 μmol/L; P < 0.001) during follow-up. Regression analysis showed that entry albumin-creatinine ratio but not smoking predicted nephropathy progression when both factors were considered together, but smoking predicted progression only when the albumin-creatinine ratio was excluded. Nephropathy progression was minimal for lower levels of albumin-creatinine ratio at entry but increased progressively for levels >300. Albumin-creatinine ratio increment during follow-up directly correlated with nephropathy progression and was greater in smokers than in nonsmokers. Unfortunately, the study investigate only the effect of active smoking. Thus, the question of whether ex-smokers and never smokers included in this study differ with regard to their renal risk remains unanswered. In my opinion, the findings of Chuahirun et al. (44) indicate that, similar to coronary artery disease (45), some subjects are resistant to the adverse renal effects of smoking as a result of a yet largely unknown genetic background. These subjects obviously do not develop albuminuria despite smoking. Thus, they also do not exhibit nephropathy progression. A genetic predisposition of smokers to develop albuminuria is suggested by the preliminary results of the Bergamo Nephrologic Diabetes Complications Trial. The DD-genotype of the ACE gene was strongly associated with microalbuminuria in smokers (46).

Evidence from Studies in Patients with Primary Renal Disease

We performed a retrospective case-control study to assess whether smoking increases the risk to progress to ESRF in patients with IgA-glomerulonephritis or autosomal dominant polycystic kidney disease (23). Because of the small sample size and modest average tobacco consumption, the subgroup of women was excluded from further analysis. 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 (OR, 10.1 [2.3 to 45]; P = 0.002). In contrast, the risk for smokers with a history of ACE inhibitor treatment was not significantly increased (OR, 1.4 [0.3 to 7.1]; P = 0.65). Another case-control study confirmed that male patients who have glomerulonephritis and smoke are at increased risk of renal function impairment (24). In this study, the negative impact of smoking was particularly marked in elderly hypertensive men. The design of these studies was retrospective, and a large prospective study is obviously needed.
Evidence from Studies in Patients with 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 >65 yr of age. Several studies have documented that the prevalence of unilateral and bilateral atherosclerotic renal artery stenosis is higher in smokers (for review, see reference 15). 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. Smoking is a known risk factor for cholesterol microembolism.

In a group of 89 normotensive, nondiabetic elderly subjects with different degrees of peripheral arteriosclerosis and no clinical signs of ischemic nephropathy, renovascular hypertension, or other nephropathies, evaluation of renal function and renal plasma flow (RPF) revealed that despite normal values for GFR, RPF declined progressively in parallel with the severity of peripheral arteriosclerosis (47). Stepwise multiple regression showed that the decrease in RPF was best explained by smoking and serum LDL cholesterol. Because there was a close association between the severity of extrarenal arteriosclerosis and renal hypoperfusion, the authors concluded that this was the result of ischemic nephropathy.

Pathohistological Findings in the Kidney of Smokers

An increase in thickness of walls of arterioles of organs not in direct contact with cigarette smoke, mainly as a result of fibroelastic intimal proliferation and hyaline thickening in the intima, has been observed in various organs of individuals without renal disease (48,49), including the kidney (50–52). 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 (53). Most of these patients had 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. As compared with nonsmokers, ever smokers exhibited more severe myointimal hyperplasia. This finding was particularly evident in patients >50 yr. 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 because women were less likely to be smokers and smoked less than half as many pack-years than did men.

The study of Lhotta et al. (53) 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 (54). Against this background, the effect of smoking is of relevance. The negative finding concerning the severity of glomerulosclerosis of course does not exclude an effect of smoking on glomerular structure. An increase in glomerular basement membrane (GBM) width in patients who have type 2 diabetes and smoke has been reported in a recent biopsy study (55). GFR was negatively correlated with heavy current smoking. The degree of interstitial fibrosis was not affected by smoking, however. The relevance of the finding of increased GBM width in smokers remains unclear, but it documents that smoking induces structural alterations even in the glomerular filter.

Using a more precise method for quantification of renal damage, our group found more severe glomerulosclerosis and tubulointerstitial fibrosis in subtotally nephrectomized rats that were treated with a cigarette smoke extract (56). Whether this is true for humans with noninflammatory renal disease as well remains to be determined.

Conclusion

The above data clearly show that cigarette 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, which presumably may have dramatic socioeconomic consequences. The adverse renal effects of smoking are particularly marked in men (especially elderly), in patients with type 1 or type 2 diabetes, in patients with a renal transplant (for review, see reference 15), and in patients with a preexisting primary renal disease.

Major efforts are needed to help patients to 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 (57). Additional psychologic support/counseling therapy is of major importance to improve further the smoking cessation success rate, which is still disappointingly limited. To the best of my knowledge, there is no information about the exact pharmaco-kinetics of sustained-release bupropion and its metabolites in patients with impaired renal function. According to the manufacturer, bupropion does not accumulate in renal failure. In contrast, nicotine accumulates in renal failure (58), which has to be taken into consideration when treating patients with nicotine replacement therapy. Unfortunately, to date, no controlled information on the success of a modern smoking cessation strategy in renal patients is available. Even in patients on renal replacement therapy, efforts to quit smoking are sorely needed to improve survival, which is substantially decreased in smokers (59,60). Of note, even among subjects who have a history of heavy smoking, the risk of coronary events can be halved by stopping the habit. This benefit from cessation of smoking is seen regardless of how long or how much a person has previously smoked (61). According to estimates, the risk of myocardial infarction can be reduced by 50 to 70% as a consequence of cessation of smoking. In contrast, the treatment of hypertension results in a reduction of risk of myocardial infarction of “only” 2 to 3% for each 1 mmHg decline in diastolic BP (62). Thus, smoking cessation is more effective...
than any antihypertensive (and lipid-lowering) treatment prescribed by a physician.

References


