Tohoku J. Exp. Med., 2001, **194**, 1–15

Review

Adverse Effects of Smoking in the Renal Patient

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Orth, S.R., Viedt, C. and Ritz, E. *Adverse Effects of Smoking in the Renal Patient*. Tohoku J. Exp. Med., 2001, **194** (1), 1–15 —— Smoking is a known risk factor for cardiovascular diseases, cancer, and several other health problems. It is the number one preventable cause of death in modern countries. The first evidence that smoking may be a renal risk factor was published in 1978. Since then, several studies documented that smoking is nephrotoxic in patients with diabetic and non-diabetic renal disease. Data from the Multiple Risk Factor Intervention Trial indicate that smoking even increases the renal risk in the general male population: an increased relative risk for end-stage renal failure (ESRF) was found for smokers as compared to non-smokers (up to 1.69 for heavy smokers). Several potential mechanisms of smoking-induced renal damage have been discussed, e.g. increase in blood pressure, alteration of intrarenal hemodynamics, as well as activation of the sympathetic nerve, the renin-angiotensin and the endothelin systems. The pathomechanisms are, however, only partly understood. Once ESRF has become established, the failure to discontinue smoking adversely affects the prognosis of patients on renal replacement therapy, mainly by increasing the risk of cardiovascular complications. Discontinuation of smoking has been shown to improve both renal and cardiovascular prognosis in the renal patient and is probably the single most effective measure to retard progression of renal failure. ——— smoking; renal failure; diabetic nephropathy; hypertension; cardiovascular complications
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Smoking is the number one preventable cause of death in modern countries (Bartecchi et al. 1994). For instance, it accounts for more than 500 000 and 400 000 deaths/year in the USA and the European Union, respectively (Bartecchi et al. 1994; Junge 1996). These numbers are currently increasing and so is tobacco consumption by adolescents, particularly by young women, who are a major target of tobacco advertisement companies (Huber and

Received November 27, 2000; revision accepted for publication May 22, 2001.
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Pandina 1997). The World Health Organization (WHO) estimated that world-wide tobacco abuse accounted for 3 million deaths in 1996 and even 10 million deaths are expected for the year 2020 (Emmons 1999). This article focuses on a less known danger of smoking, i.e., the adverse renal effects of smoking. Furthermore, we discuss the increase in cardiovascular risk in the renal patient related to smoking.

Influence of smoking on albuminuria and the risk of end-stage renal failure in subjects without primary renal disease (Table 1)

Smoking emerged as an independent predictor of (micro)albuminuria in several studies which examined otherwise healthy patients with primary hypertension (Orth 2000). The hypothesis of a nephrotoxic effect of smoking is further supported by a cross-sectional study in 7476 non-diabetic subjects in Groningen, The Netherlands (Pinto-Sietsma et al. 2000). The study documents that the urinary albumin excretion rate is correlated to the amount of cigarettes smoked per day. After adjustment for several potential confounding factors, subjects who smoked ≦20 cigarettes/day and subjects who smoked >20 cigarettes/day, respectively, showed a dose-dependent association between smoking and high normal albuminuria (relative risk, 1.33 [95% CI, 1.10-1.61] and 1.98 [CI, 1.49-2.64]) and microalbuminuria (relative risk, 1.92 [CI, 1.54-2.39] and 2.15 [CI, 1.52-3.03]). Halimi et al. (2000) confirmed a marked risk of irreversible proteinuria that may occur despite moderate smoking in a study on 28 409 subjects of the general population. Recently, Regalado et al. (2000) performed a prospective study including 51 patients with primary hypertension for a mean follow-up of 35.5 months. Despite reduction of mean arterial blood pressure from 126.8±1.3 to 96.5±1.1 mmHg, plasma creatinine increased from 1.5±0.1 to 1.9±0.2 mg/100 ml. Factors that independently predicted renal functional decline were smoking, greater initial plasma creatinine level, and black ethnicity. Of interest, smoking was by far the most powerful predictor of renal functional decline and the only one which is potentially remediable.

Data from the Multiple Risk Factor Intervention Trial (MRFIT) including 332 544 men indicate that smoking increases the renal risk in the general male population: an increased relative risk for end-stage renal failure (ESRF) was found for smokers as compared to non-smokers (up to 1.69 for heavy smokers) (Whelton et al. 1995; Klag et al. 1997). The increase in risk was independent of age, ethnicity, income, blood pressure, diabetes mellitus, prior history of myocardial infarction, or serum cholesterol. These findings have recently been confirmed in an elderly nondiabetic population: during a minimum observation time of 3 years the number of cigarettes smoked was highly associated with an increase in serum creatinine ≧0.3 mg/100 ml (Bleyer et al. 2000). Other studies, however, did not find an adverse effect of smoking

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

- Number of cigarettes smoked correlates with urinary albumin excretion rate in healthy subjects
- Independent predictor of (micro) albuminuria in patients with primary hypertension
- Most powerful predictor of renal functional decline in primary hypertension
- Number of cigarettes smoked dose-dependently increases the risk of ESRF in the male general population
- In type 1 and type 2 diabetes mellitus: independent risk factor for the onset of microalbuminuria, for progression of microalbuminuria to manifest proteinuria (i.e., diabetic nephropathy) and for acceleration of the rate of progression of diabetic nephropathy to ESRF
- Increased risk for progression to ESRF in primary renal diseases
- Increased risk for progression of chronic transplant nephropathy (?)

ESRF, end-stage renal failure.

on renal function (Perry et al. 1995a; Halimi et al. 2000). It is thus of major interest to analyze the effect of smoking in patients with renal diseases, because this population may be particularly susceptible to smoking-related renal damage.

Smoking and diabetic nephropathy (Table 1)

Christiansen (1978) reported that smoking was a risk factor for diabetic nephropathy. This was the first report about a nephrotoxic effect of smoking. Since then, several studies confirmed an increased renal risk in patients with both type 1 and type 2 diabetes who smoke. Smoking (i) increases the risk to develop microalbuminuria, (ii) accelerates the rate of progression from microalbuminuria to manifest proteinuria, and (iii) accelerates progression of renal insufficiency to ESRF (Orth 2000). Probably, the most important adverse effect of smoking is acceleration of the rate of progression of renal failure. Sawicki et al. (1994) calculated the adjusted odds ratio for progression of diabetic nephropathy, defined as an increase in proteinuria >20% per year and/or a reduction of glomerular filtration rate (GFR) > 20%. The odds ratio was higher by a factor of 2.74 for each 10 cigarette pack years. In this study all patients were on intensified insulin and antihypertensive therapy, so that confounding effects of hyperglycemia and hypertension are minimized. In a study of Biesenbach et al. (1994) the rate of loss of GFR was higher by a factor of 1.44 and 1.66 in smoking as compared to non-smoking patients with type 1 and type 2 diabetes, respectively.

It is of major interest that smokers are at greater risk to develop type 2 diabetes (Perry et al. 1995b; Rimm et al. 1995; Nakanishi et al. 2000). In a recent prospective cohort study on 1266 non-diabetic males aged 35–59 years Nakanishi et al. (2000) found that the relative risk to develop impaired fasting glucose during 5 years of observation was 1.62-fold higher in ever-smokers as compared to never-smokers. The relative risk to develop type 2 diabetes was dose-dependent: 1–20 cigarettes/day=1.88 (CI: 0.71–5.0), 21–30 cigarettes/day=3.02 (CI: 1.15–7.94), ≧31 cigarettes/day=4.09 (CI: 1.62–10.29). The increased risk may be related to the fact that smoking aggravates insulin resistance in healthy smokers, at least according to some studies (Orth 2000).

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. Furthermore, the number of cigarettes smoked daily and the number of pack-years of exposure seem to be associated with development of impaired fasting glucose and type 2 diabetes (Nakanishi et al. 2000).

Smoking and non-diabetic renal disease (Tables 1–3)

In patients with autosomal dominant polycystic kidney disease (ADPKD) Chapman et al. (1994) found that individuals with established proteinuria had not only higher mean arterial pressure and more aggressive development of renal cysts, but had also a greater pack year smoking history than did their nonproteinuric counterparts. In lupus nephritis, a retrospective cohort study of 160 patients with a median follow-up of 6.4 years documented that smoking at the time of onset of nephritis was an independent risk factor for more rapid progression to ESRF (Ward and Studenski 1992). The median time interval to ESRF was 145 months in smokers and in excess of 273 months in non-smokers. This observation is particularly important, because the effect of smoking was independent of hypertension and immunosuppressive treatment.

Since there was no definite information on a potential nephrotoxic effect of smoking in primary renal disease, we performed a retrospective matched case-control study (Orth et al. 1998). This European multicenter study was designed to assess whether in patients with

TABLE 2. *Crude smoking-associated risk of ESRF in 144 male patients with IgA-glomerulonephritis or autosomal dominant polycystic kidney disease* (*Orth et al. 1998*)

Pack-years	Cases (*n*, [%])	Controls (*n*, [%])	Odds ratio	95%-confidence interval	*p*-value†
0–5	26 (36)	47 (65)	1.0	—	—
5–15	17 (24)	11 (15)	3.5	1.3–9.6	0.017
>15	29 (40)	14 (19)	5.8	2.0–17	0.001

†(Wald χ^2).

IgA-glomerulonephritis (IgA-GN) and ADPKD tobacco consumption increased the risk to progress to ESRF. Because analysis of tobacco consumption (given as pack-years [PY]) showed no strata inhomogeneity between renal diseases, IgA-GN and ADPKD were pooled for statistical analysis. Due to small sample size and modest average tobacco consumption, the subgroup of women was excluded from further analysis. Table 2 shows the distribution of cigarette smoking in male patients; consumption of cigarettes was subdivided into three categories, i.e., 0–5, 5–15 and >15 PY. The crude estimators for different quantitative levels of smoking document a dose-dependent increase in the risk to be in ESRF in male smokers as compared to non-smokers or moderate smokers (0–5 PY). After adjustment for possible confounders, multivariate analysis revealed that the risk to be in ESRF was substantially higher in male smokers with no history of angiotensin converting enzyme (ACE) inhibitor treatment. In contrast, the odds ratio for smokers with a history of ACE inhibitor treatment was not significantly increased (Table 3). A recent case control study confirmed that male patients with glomerulonephritis who smoke are at increased risk of renal function impairement (Stengel et al. 2000).

Since the design of these studies was retrospective, a prospective study would be helpful to confirm the results (Samuelsson and Attman 2000). The fact that we (Orth et al. 1998) and Stengel et al. (2000) did not find an adverse effect of smoking on renal function in small female subgroups is presumably related to the limited sensitivity of the studies; certainly the data do not permit to completely rule out an adverse effect of smoking on renal prognosis in women.

Smoking and renal transplantation (Table 1)

Most studies published to date indicate a lack of correlation of cardiovascular risk factors such as smoking with the development of chronic allograft nephropathy in humans (Hegeman and Hunsicker 1995). A recent retrospective analysis of Kasiske and Klinger

TABLE 3. *Smoking-associated risk of ESRF* (*stratified for ACE-inhibitor treatment and adjusted for systolic blood pressure*) *in 144 male patients with IgA-glomerulonephritis or autosomal dominant polycystic kidney disease* (*Orth et al. 1998*)

Pack-years	ACE-inhibitor			No ACE-inhibitor		
	Odds ratio	95%-confidence interval	*p*-value†	Odds ratio	95%-confidence interval	*p*-value†
<5	1.0	—	—	1.0	—	—
>5	1.4	0.3–7.1	0.65	10.1	2.3–45	0.002

†(Wald χ^2).

(2000) noted a higher rate of graft loss in renal graft recipients. This was mainly accounted for by cardiovascular death with a functioning graft. In an ongoing prospective study, this issue is currently adressed by G. Opelz (Heidelberg, Germany). A preliminary retrospective analysis of Opelz suggests that smoking by itself adversely affects late graft function, even if corrections are made for cardiovascular death with a functioning graft (personal communication). A similar analysis was performed by the group of L.C. Paul (2000) and yielded the same results. We have to wait for the final results of these investigations in order to give a definite answer to the question whether smoking plays a role in renal allograft failure.

The effect of smoking on renal allograft function may depend on the primary renal disease which had led to ESRF. In patients who had reached ESRF as a result of lupus nephritis, the risk of renal transplant loss was substantially increased in smokers (Stone et al. 1998). In this study, smoking demonstrated both the strongest association and the highest relative risk for allograft loss (relative risk 2.5, $p < 0.0001$) as compared to the other factors which confered an increased risk for allograft loss, i.e., delayed graft function, acute rejection episodes, and total HLA mismatches. Lupus erythematosus represents only a small subgroup of renal transplanted patients and a specific disease entity, but the above results are of major clinical importance and point to the possibility that the alterations of the immune response reported in smokers (Orth et al. 1997) may be particularly detrimental in secondary renal diseases related to major immune defects such as lupus erythematosus.

Potential mechanisms of smoking-induced renal damage (Table 5)

Several potential mechanisms of smoking-induced renal damage have been discussed (Orth 2000), but the precise nature of the nephrotoxic

TABLE 4. *Potential pathomechanisms of smoking-induced renal injury*

- Increased sympathetic nerve activity
- Increase in blood pressure and heart rate
- Alteration of diurnal blood pressure rhythm
- Increase in renal vascular resistance leading to decrease in GFR and RPF (ET-1?)
- Arteriosclerosis of the renal arteries and the intrarenal arteries and arterioles (ET-1?)
- ET-1-mediated proliferation and matrix accumulation of VSMC, endothelial cells and mesangial cells
- Tubulotoxicity
- Direct toxic effects on endothelial cells
    - Alteration of the prostaglandin/thromboxane metabolism
    - Oxidative stress through generation of reactive oxygen species
    - Nitric oxide depletion
    - Impairement 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 immune response
- Antidiuresis (vasopressin)
- Increased insulin resistance

ET-1, endothelin-1; GFR, glomerular filtration rate; RPF, renal plasma flow; VSMC, vascular smooth muscle cells.

Table 5. *Contrasting effects of smoking on renal hemodynamics in volunteers and patients with IgA glomerulonephritis* (*Ritz et al. 1998*)

	GFR	FF	RVR	MAP
volunteers ($n=15$)				
−basal	120±17.7	21.3±4.24	97.6±27.2	92.8±8.98
−smoking	102±19.3[b]	17.4±3.41[b]	108±30.4[c]	105±7.78[d]
IgA-GN ($n=7$)				
−basal	109±18.3	19.8±4.14	97.9±17.6	92.3±12.1
−smoking	111±34.0	18.9±6.32	116±38.6	105±13.0[a]

GFR, glomerular filtration rate; FF, filtration fraction; RVR, renal vascular resistance; MAP, mean arterial pressure.
[a] $p<0.005$, intraindividual differences basal vs. smoking by paired t-test.
[b] $p<0.001$, intraindividual differences basal vs. smoking by paired t-test.
[c] $p<0.006$, intraindividual differences basal vs. smoking by paired t-test.
[d] $p<0.0001$, intraindividual differences basal vs. smoking by paired t-test.

effect of smoking is unknown. Against the background of "light cigarettes" with low nicotine content and regular cigarettes with moderate or high nicotine content it is of particular interest to differentiate between smoking-induced renal damage due to nicotine per se and/or other (partially unknown) components of cigarette smoke. There is no doubt that the present data do not allow to give a definite answer which substances in cigarette smoke are responsible for the adverse renal effects of smoking, but some potential pathomechanisms seem to be linked to nicotine per se.

Potential adverse renal effects of smoking linked to nicotine

Increase in sympathetic activity and blood pressure. Since the first decade of the 20th century it has been known that smoking induces a transient increase of BP and heart rate (Hesse 1907). This increase in BP and heart rate seems to be related to nicotine per se, since no such changes occur when nicotine-free cigarettes are smoked (Aronow et al. 1971). Today we know that these acute hemodynamic effects are mediated mainly via sympathetic activation and vasopressin release. In addition, in patients with primary hypertension an increase in cortisol, adrenocorticotrophic hormone (ACTH) and plasma aldosterone concentration has been noted during smoking (Orth 2000).

Grassi et al. (1994) demonstrated that nicotine increases sympathetic activity via direct stimulation of postganglionic sympathetic nerve endings: smoking a single cigarette markedly increased plasma concentrations of norepinephrine and epinephrine in healthy volunteers, whereas postganglionic muscle sympathetic nerve traffic decreased significantly. Thus, nicotine directly stimulates catecholamine release from peripheral sympathetic nerve endings and the adrenal medulla (Haass and Kübler 1996). Increased sympathetic activity may also accelerate progression of renal failure (Amann et al. 2000; Orth et al. 2001). It is thus plausible to assume that a further increase of catecholamine release from peripheral sympathetic nerve endings induced by smoking in subjects with renal disease may damage the kidney via two mechanisms, i.e., indirectly through BP elevation, but also as a direct result of activation of the sympathetic system (Amann et al. 2000; Orth et al. 2001).

In view of the importance of BP on the evolution of renal diseases, the effects of smoking on BP are of considerable interest. Ambulatory BP measurements documented that smoking in parallel with the stimulation of the

sympathetic system causes a significant, but transient increase (lasting 30 minutes) of BP in healthy (Minami et al. 1999) and hypertensive subjects (Mann et al. 1991; Groppelli et al. 1992). This was also found in patients with type 2 diabetes (Poulsen et al. 1998) or primary renal disease (Ritz et al. 1998).

Smoking also seems to alter the diurnal rhythm of BP. Hansen et al. (1994) reported that the night/day ratio of systolic and diastolic BP in healthy smokers was lower than in non-smokers. In one study a derangement of the diurnal rhythm of BP was not found in patients with type 1 diabetes who smoked (Hansen et al. 1994). In contrast, in a preliminary communication Barna et al. (1996) reported decreased ratios of daytime to nighttime BP in smoking healthy volunteers and in subjects with type 1 diabetes. Since the deleterious role of elevated BP, particularly at night-time, on progression of renal diseases is well known, the intermittent (daytime) and, even worse, persistent (nighttime) increase in BP induced by smoking may well contribute to progression of diabetic and non-diabetic renal disease. This possibility is particularly pertinent, since an even minor increment in BP accelerates the rate of progression (Klahr et al. 1994).

Alteration of intrarenal hemodynamics. Ritz et al. (1998) performed a study in healthy volunteers to investigate the effects of smoking on the healthy kidney: smoking (as compared to sham-smoking) caused a significant decrease in GFR, filtration fraction (FF) and renal plasma flow (RPF) as measured by radioisotope infusion clearance. Renovascular resistance increased significantly. The FF is a surrogate marker of glomerular capillary pressure. This parameter decreased in healthy volunteers. At first sight this observation may appear paradoxical, since reduced intraglomerular pressure should provide nephroprotection, but the renal response is apparently different in subjects with and without renal disease. The findings of Ritz et al. (1998) concerning GFR and RPF were confirmed by Halimi et al. (1998) in non-smokers who chewed a nicotine chewing gum. Interestingly, renal vasoconstriction did not occur in smokers. The authors concluded that smokers continue to exhibit the systemic response to nicotine, i.e., an increase in BP and heart rate, but are tolerant to the renal effects of nicotine. The latter was attributed to a compensatory increase of the synthesis of cyclic guanosine monophosphate (cGMP) in the kidney of smokers as indicated by increased urinary excretion.

Ritz et al. (1998) also compared the renal hemodynamic effects of smoking in volunteers with those in patients with IgA glomerulonephritis. As shown in table 4, whilst the increase in mean arterial pressure and heart rate was similar in patients with IgA-GN and volunteers, a significant decrease in GFR and filtration fraction was not demonstrable in patients with IgA-GN, in contrast to what was seen in volunteers. During smoking, a significant increase in the urinary albumin/creatinine ratio was noted, further pointing to an adverse effect of smoking on glomerular capillary pressure.

Taken together these findings are consistent with the hypothesis that in patients with glomerular diseases, in whom the preglomerular vasculature is presumably vasodilated, smoking-induced vasoconstriction is unable to overcome vasodilation. As a result one would expect that the increase in systemic pressure is transmitted partially to the glomerular microcirculation, causing acute glomerular hypertension. As reported recently by Benck et al. (1999) pretreatment with the α-adrenergic blocker prazosin (compared to placebo) failed to affect the change in renal hemodynamics, whilst pretreatment with the β-blocker atenolol obliterated the renal hemodynamic response.

Activation of the renin-angiotensin system. Based on the study of Benck et al. (1999) we propose the following hypothesis (Fig. 1): Smoking acutely increases circulating catecholamines and potentially also efferent sympathetic traffic

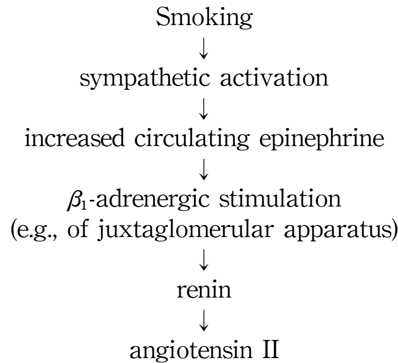

Fig. 1. Hypothetical sequence of smoking-induced activation of the renin-angiotensin system as one major pathomechanism of the adverse renal effects of smoking.

to the kidney. Renin secretion is stimulated via β-1-adrenergic stimulation of the juxtaglomerular apparatus, thus increasing the concentration of angiotensin II. It is possible, but currently unproven, that angiotensin II is involved in mediating the distal effects of β-adrenergic stimulation. This hypothesis would explain the observation in our retrospective case control study that an increased renal risk was no longer demonstrable when smokers were treated with ACE inhibitors (Orth et al. 1998) (Table 2). A further explanation why ACE inhibition apparently protects against smoking-induced renal function alteration is the improvement of vascular dysfunction when smokers are treated with an ACE inhibitor (Chalon et al. 1999). In vitro data suggest that this effect is partly mediated by scavenging free radicals and by attenuation of the cigarette-induced suppression of nitric oxide production (Ota et al. 1997).

Activation of vasopressin. In 1945, Burn et al. (1945) reported that nicotine exerts an antidiuretic action in rats and in humans. In rats of approximately 190 g body weight, subcutaneous injection of a rather high dose of nicotine (0.25 mg) induced an initial diuresis during the 15 minutes post injection; this was followed by an inhibition of the diuresis for about 45 minutes as compared to control rats. The authors interpreted the short increment in diuresis as a result of the nicotine-induced initial rise in BP. When the pituitary gland was removed, no such inhibition of diuresis occurred. These results were confirmed in dogs by Cadnapaphornchai et al. (1974) who found that nicotine increases vasopressin release by altering cervical parasympathetic tone. Similar to their observations in the rat, Burn et al. (1945) reported that in men diuresis began at the time when they started to smoke. Inhibition of diuresis then occurred after 15 minutes of smoking, and the effect of three cigarettes induced nearly complete inhibition of diuresis during 2.5 hours, after which the diuresis began again to reach a peak (4.5 hours). In some subjects an antidiuretic effect was noted after smoking only one cigarette. The antidiuretic effect of smoking was quite variable between individuals. Antidiuresis is probably due to increased vasopressin secretion during smoking. In this context it is of interest that antidiuresis has been proposed as a potential pathogenetic factor in progression of chronic renal failure (Bankir and Bouby 1991). As to the mechanism involved, it has been proposed that vasopressin increases single nephron GFR inappropriately via modulating the activity of the tubuloglomerular feedback. This was thought to result from changes in urea recycling (Bankir and Bouby 1991).

Potential adverse renal effects of smoking linked to substances in cigarette smoke other than nicotine

Toxic effects on the endothelium. Cigarette smoking dose-dependently impairs endothelial cell dependent vasodilatation in healthy individuals (Celermajer et al. 1993). Endothelial cell dependent and independent relaxation induced by endogenous vasodilators is impaired in smokers (Rångemark and Wennmalm 1992). Endothelial cell dysfunction is an early feature of atherosclerosis and is also implicated in the genesis of glomerular injury. Disturbed active vasodilation is deleterious for coronary arteries

(Kyriakides et al. 1992; Egashira et al. 1993) and might be important in the genesis of altered renal hemodynamics and renal functional parameters of smokers (Halimi et al. 1998; Ritz et al. 1998; Gambaro et al. 1998; Benck et al. 1999).

Hyperfiltration in diabetic nephropathy. Concerning intrarenal hemodynamics in insulin-treated diabetics, Ekberg et al. (1990) reported a significantly higher prevalence of glomerular hyperfiltration (41% vs. 18%) in smokers than in non-smokers. Furthermore, the GFR was directly dependent on the intensity of smoking. The fact that this correlation was not found in users of snuff was interpreted to indicate that the renal changes are caused by a substance in tobacco smoke other than nicotine which is absorbed by the nasal mucosa when snuffing. The increment of GFR induced by smoking may play a role in the genesis of hyperfiltration as a potential mediator of accelerated progression of chronic renal disease (Hostetter 1995). Smoking further increases the hyperfiltration that is observed in early stages of diabetic nephropathy.

Oxidative stress. Oxidative stress is probably another major player in the genesis of smoking-induced vascular renal injury. Extrusion of glutathione from endothelial cells and activation of the hexose monophosphate shunt, which is necessary to maintain glutathione in the reduced state, point to the presence of oxidative stress, which may be imposed by the free radicals that are present in tobacco smoke (Noronha-Dutra et al. 1993). The concentrations of antioxidant enzymes such as glutathione peroxidase, catalase and superoxide dismutase decrease and markers of oxidative stress increase as renal insufficiency advances (Mimic-Oka et al. 1999). The patient with renal insufficiency may thus be particularly susceptible to additional oxidative stress induced by smoking. Plasma extracellular superoxide dismutase, a major superoxide scavenger, is independently associated with a history of myocardial infarction. It is much lower in current smokers as compared to ex-smokers and non-smokers (Wang et al. 1998).

Nitric oxide. The inhibitory effect of smoking on nitric oxide generation may play a critical role in increasing renal vasculature tone. In addition, intrarenal arterial dilation in response to nitric oxide is significantly impaired in type 2 diabetic patients, as recently documented by Matsumoto et al. (1999). Nitric oxide depletion in smokers may also promote vascular smooth muscle cell and mesangial cell proliferation. This hypothesis is based on two observations: first, increased expression of inducible nitric oxide synthase (iNOS) in a gene transfer strategy has been reported to inhibit neointimal hyperplasia after ballon angioplasty (von der Leyen et al. 1995); second, inhibition of iNOS in a rat model of aortic allograft arteriosclerosis increases intimal thickening (Shears et al. 1997). A genetic approach to explain the different susceptibility of individuals to smoking-induced organ damage has been proposed by Wang et al. (1996): 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 (Wang et al. 1996). Whether a similar genetic susceptibility determines an increased renal risk in smokers is an issue that deserves further investigation.

Activation of the endothelin (ET) system. Nephromegaly and glomerulomegaly are known risk factors for progression. It is therefore remarkable that in 1031 subjects aged 40–60 years, smoking and fasting blood glucose concentration were the most significant factors associated with enlarged kidney size by multivariate analysis (Päivänsalo et al. 1998). Moreover, renal size increased with PY of smoking. These findings argue for increased generation of growth factors in the kidneys of smokers. Besides angiotensin II (see above),

another growth factor involved may be ET-1. ET-1 plasma concentrations are increased in smokers (Orth 2000). ET-1 is a likely candidate, because it induces the full spectrum of functional (increase in renal vascular resistance) and morphologic (nephrosclerosis) alterations observed in smokers. Smoking may activate the ET-system via several pathways. ET-1 can be directly activated by angiotensin II and vasopressin (Emori et al. 1989). Furthermore, 8-Iso-prostaglandin $F_2\alpha$, a member of the F_2-isoprostanes which is increased in the plasma of smokers (Morrow et al. 1995), increases ET-1 mRNA and ET-1-dependent proliferation of endothelial cells in vitro (Yura et al. 1999). Other potential factors are carbon monoxide-induced hypoxia, nicotine-induced α-adrenergic stimulation and oxygen free radical generation (Remuzzi 1999).

Toxic effects on tubular cells. Another potential pathogenetic mechanism of smoking-induced renal damage is alteration of proximal tubular function and proximal tubular damage in smoking diabetic and non-diabetic subjects (Buchet et al. 1990; Hultberg et al. 1992; Wong et al. 1992). Tubular cell dysfunction may conceivably contribute to tubulointerstitial injury and progression. These alterations of proximal tubular function include increased urinary excretion of N-acetyl-β-glucosaminidase (NAG) (Buchet et al. 1990; Hultberg et al. 1992), impairment of organic cation transport (Wong et al. 1992), and, as indirect evidence for tubular damage, reduction of ^{99m}technetium-mercaptoacetyltriglycine (MAG_3) clearance (Gambaro et al. 1998). Preliminary data of our group confirm that in an animal model exposure to tobacco leads to tubulointerstitial damage (unpublished observation).

Reversibility of smoking-induced renal damage

The question arises whether cessation of smoking reverses the renal risk. One study in patients with type 1 diabetes and nephropathy provided convincing evidence in this respect (Chase et al. 1991): in patients with adequate control of BP and glycemia, progression was considerably less in patients who had stopped smoking. In another study, progression was found in 53% of current smokers, 33% of ex-smokers and 11% of non-smokers (Sawicki et al. 1994). Furthermore, albuminuria significantly decreased in patients with type 1 diabetes when patients stopped smoking (Chase et al. 1991). It is plausible to assume that this may also be true in non-diabetic renal diseases. Pinto-Sietsma et al. (2000) recently reported that only a minor increased relative risk for microalbuminuria is noted in non-diabetic subjects who were former smokers. These former smokers had no changes in GFR. Thus, it can be concluded that smoking-induced renal damage is, at least in part, reversible.

Consequences for the treatment of the renal patient

The above data clearly document that smoking is a major renal risk factor in diabetic and non-diabetic renal disease. Discontinuation of smoking is probably the single most effective measure to retard progression of renal failure. Major efforts have to be undertaken to help the patient to quit smoking, including newer approaches such as therapy with sustained-release bupropion and nicotine patches (Jorenby et al. 1999). Close monitoring of the patient is imperative, especially because smokers are less compliant than non-smokers (McNagy et al. 1997). Even if ESRF is reached smoking should be discontinued. There is solid evidence that cessation of smoking reduces the risk of premature death due to cardiovascular complications. Physicians should always be aware of the fact that "persuading hypertensive patients not to smoke is the single most effective measure we can take to reduce their risk" (Sleight 1993). It has been estimated that the risk of myocardial infarction can be reduced by 50–70% as a consequence of cessation of smoking. In contrast, the treatment of hypertension

results in a reduction of risk of myocardial infarction of "only" 2–3% for each 1 mmHg decline in diastolic BP (Manson et al. 1992). Smoking is the strongest predictor of mortality in type 2 diabetes (Gambara et al. 1997). According to lifetable analyses, smoking cessation will prolong the life of a 45-year-old smoking, hypertensive, diabetic male by 4–5 years; the treatment of hypertension is estimated to prolong the life of the same individual by only 1 year (Yudkin 1993). The risk of cardiovascular death is particularly high in diabetic patients with ESRF who smoke (Stegmayr and Lithner 1987; Stegmayr 1990) and may be aggravated by cumulation of nicotine in patients with renal failure (Molander et al. 2000). In dialysed patients with type 1 diabetes smoking has been shown to increase the relative risk of myocardial infarction by a factor of 2.6 (Koch et al. 1993). This has also been confirmed in hemodialyzed patients with type 2 diabetes. The risk of atrial fibrillation, a frequent arrythmia in hemodialysis patients, appears to be associated to coronary heart disease and may contribute to cardiovascular morbidity and mortality in ESRF (Fabbian et al. 2000). Lower serum albumin concentrations predict increased mortality in hemodialysis patients. According to a recent study, baseline serum albumin is significantly lower in active as compared to non-smokers on hemodialysis (Leavey et al. 2000). Smoking is a risk factor for systolic dysfunction in dialysis patients (Parfrey and Harnett 1994). Furthermore, smoking increases (i) the risk of death during the first 90 days on hemodialysis (Khan et al. 1995), (ii) the risk of cerebrovascular accident in patients with chronic renal failure (Ishikawa 1994), (iii) the risk of early and late fistula failure (Wetzig et al. 1985), and (iv) the risk of permanent change from continuous peritoneal dialysis to hemodialysis due to complications (Gokal et al. 1987). We conclude that "smoking cessation is still the best medicine" (Hays et al. 1998), and this is particularly true for patients with renal disease.

Acknowledgments

The data of references (Orth et al. 1998) and (Ritz et al. 1998) are reprinted by permission of Blackwell Science Inc. and Lippincott Williams & Wilkins, respectivelys.

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