Smoking and the kidney

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Introduction

Amongst the health hazards of smoking carcinogenesis [1], cardiovascular disease [1,2] and lung disease [1,3] have attracted considerable attention. In contrast, until recently the potential impact of smoking on renal function and renal disease have remained largely unnoticed [4]. Admittedly, the number of patients with smoking-related renal problems is considerably smaller than the number of patients with malignancy, cardiovascular or pulmonary problems, but in view of the high cost of renal replacement therapy the problem is by no means trivial. Certainly the consequences for the health budget are quite considerable [4].

There is no doubt that smoking promotes atherogenesis in various vessels including the abdominal aorta [5] and, by implication, plays a prominent role in the genesis of atherosclerotic renal artery stenosis and ischaemic nephropathy [6–8]. There is also convincing evidence that smoking is one causal factor in the genesis of renal cell carcinoma [9] and uroepithelial cell carcinoma [10,11]. We shall restrict, however, the discussion to the repercussions of smoking on renal function in subjects without renal disease and in patients with primary renal disease.

The acute effects of smoking on the kidney

Smoking causes intense sympathetic excitation [12] paralleled by an increase in blood pressure (up to 21 mmHg systolic [13]), tachycardia and increased concentrations of catecholamines in the circulation. Vasoconstriction is noted in many vascular beds, i.e. the coronary circulation or the forearm. It comes as no surprise that in healthy volunteers acute smoking (compared to sham smoking) causes an increase in renovascular resistance of 11% as well [14]. This is accompanied by a decrease in glomerular filtration rate (GFR) (−15%) and filtration fraction (−18%) [14]. The effect is presumably due to nicotine per se, since the findings can be reproduced by chewing nicotine-containing gum [14]. Based on indirect data it has been concluded that in the healthy individual, smoking causes afferent vasoconstriction, presumably protecting the glomerulus against the acute rise in blood pressure. In contrast, in the patient with renal disease, preglomerular vessels are vasodilated. Apparently smoking-induced vasoconstriction is unable to overcome vasodilation, so that the smoking-induced increase in blood pressure can be transmitted into the glomerulus, causing glomerular hypertension [14]. This hypothesis requires further confirmation. A recent analysis [15] shows that the renal haemodynamic effects can be obliterated by pretreatment with β-blockers. Renal haemodynamic effects of smoking are apparently caused by β-adrenergic stimulation, either directly via increased circulating epinephrine, or indirectly via β-adrenergically mediated increase in local angiotensin II concentrations. The idea that circulating catecholamines are involved would make sense, since efferent sympathetic nerve traffic, at least to the N. suralis, is decreased, presumably as a consequence of a baroreceptor-mediated response to elevated blood pressure [16].

The chronic effects of smoking on the kidney

Until now, no information on this aspect had been available, but recently some interesting results have been reported. Gambaro et al. [17] noted that renal plasma flow, but not GFR, was lower in chronic smokers compared to non-smokers. This was associated with modest elevations in plasma endothelin concentrations. Thus, smoking appears to induce functional abnormalities of the renal vasculature and this

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is complemented by observations on anatomical abnormalities of intrarenal vasculature of smokers [7,8]. It is of interest that GFR was not found to be decreased and this may point to compensatory hyperfiltration of residual nephrons, although other explanations are not excluded. This hypothesis has recently been discussed by Remuzzi [18] and would be in line, amongst others, with the observation that smoking turned out to be a potent predictor of albuminuria in epidemiological studies [19–21].

What is currently unknown is how such renal damage in chronic smokers without primary renal disease is mediated. Whilst the acute effects mediated via sympathetic activation are impressive [14], one has to consider alternative possibilities of how long-term injury to the kidney is mediated. In analogy with other vascular beds, endothelial cell damage [22] appears to play a major role, but complementary possibilities, such as altered prostaglandin metabolism (increased thromboxane, increased isoprostanes), diminished nitric oxide and increased endothelin production, increased interaction with and aggregation of platelets, PMN and monocytes, hypoxic damage from carbon-monoxide and many others are not excluded. This is a fertile field for further research. The idea of altered nitric oxide handling in the kidney of smokers finds further support in the study of Halimi et al. [23], who assessed the response of effective renal plasma flow (ERPF) and urinary cyclic guanosine monophosphate (cGMP) as an index of nitric oxide action to a 4 mg nicotine gum in non-smokers and chronic smokers. In non-smokers ERPF and GFR decreased by 15% and 14%, respectively, and urinary cGMP decreased by 51%. In contrast, ERPF and GFR remained unchanged in chronic smokers and cGMP rose by 87%. Since changes in ERPF induced by nicotine were positively correlated with changes in urinary cGMP the authors interpreted that increased cGMP and nitric oxide are responsible for renal tolerance to nicotine in chronic smokers.

The effects of smoking on development and progression of diabetic nephropathy

Diabetologists were the first to notice that patients with type 1 diabetes who had smoked more frequently microalbuminuria and overt diabetic nephropathy [24], finding that meanwhile has been confirmed by numerous subsequent investigators [4]. Smoking increases the risk to develop microalbuminuria (relative risk 2.8! [25]), shortens the interval from microalbuminuria to overt nephropathy [26] and accelerates progression of nephropathy and loss of GFR. Biesenbach et al. [27] noted that the rate of loss of measured endogenous creatinine clearance was nearly twice as high in smoking compared to non-smoking type 1 or type 2 diabetic patients: the rate of loss of GFR in patients with type 1 diabetes was 0.86±0.31 ml/min/month in non-smokers, but 1.24±0.29 ml/min/month in smokers; the respective values for patients with type 2 diabetes were similar, i.e. 0.73±0.38 ml/min/month and 1.21±0.34 ml/min/month.

Matters are somewhat more complex in type 2 diabetes, since smoking also increases the risk of subjects to develop type 2 diabetes, possibly because it increases insulin resistance [4]. Nevertheless, the risk of smokers to develop microalbuminuria and acceleration of the progression of nephropathy has been equally well documented in type 2 as in type 1 diabetes.

What is particularly encouraging, however, is the observation of Sawicki et al. [28] that in patients with type 1 diabetes who had well-controlled HbA1c and blood pressure, the rate of loss of measured GFR was considerably lower in ex-smokers compared to current smokers, i.e. 33% vs 53%. This observation suggests that benefit can be derived from cessation of smoking, even in patients with established diabetic nephropathy.

The effects of smoking on progression in patients with non-diabetic renal disease

There has been a report [29] that in patients with lupus nephritis, smoking at the time of onset of nephritis was an independent risk factor for the more rapid development of end-stage renal disease, independent of immunosuppressive or antihypertensive therapy. Furthermore, a preliminary observation in the Multiple Risk Factor Intervention Trial suggested a higher risk of end-stage renal failure in smokers compared to non-smokers [30]. Orth et al. [31] provided strong biostatistical evidence that smoking accelerates progression in patients with different forms of inflammatory or non-inflammatory primary renal disease. The salient findings of this report are summarized in Table 1. A matched pair analysis was performed in patients with either IgA glomerulonephritis or autosomal dominant polycystic kidney disease comparing patients on maintenance haemodialysis with patients of the outpatient clinic who did not require renal replacement therapy (serum creatinine <3 mg/dl). Matching criteria were renal disease, gender, region of residence, and age at renal death of cases. The number of female patients was too small for statistical analysis, but in male smokers, a dose-dependent increase of the odds ratio, i.e. the risk to be on renal replacement therapy, was noted. Consequently, there can be no doubt that smoking aggravates the evolution of primary renal diseases. It is currently unresolved whether interference with the acute haemodynamic effects of smoking, particularly lowering of blood pressure, attenuates the adverse effects of smoking, but the observation is encouraging that ACE inhibitor treatment apparently abrogates the renal risk of smoking (Table 1).

Recently, Kasiske and Klinger [32] noted higher graft loss in renal transplanted patients; in his retrospective analysis, this was accounted for by cardiovascular death with functioning grafts. In an ongoing prospective study, this issue is currently addressed by us in collaboration with G. Opelz (Heidelberg, Germany), but a preliminary retrospective analysis of
Tobacco-associated risk (stratified for ACE-inhibitor treatment and adjusted for systolic blood pressure) to be in end-stage renal failure in male patients with IgA glomerulonephritis ($N = 44$ pairs) and autosomal dominant polycystic kidney disease ($N = 28$ pairs). [31]

<table>
<thead>
<tr>
<th>Pack-years</th>
<th>ACE inhibitor</th>
<th>No ACE inhibitor</th>
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<tbody>
<tr>
<td></td>
<td>Odds ratio</td>
<td>95% confidence interval</td>
</tr>
<tr>
<td>&lt;5</td>
<td>1.0</td>
<td>–</td>
</tr>
<tr>
<td>&gt;5</td>
<td>1.4</td>
<td>0.3–7.1</td>
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*($Wald^2$).

Opelz suggests that smoking by itself adversely affects late graft function, even if corrections are made for cardiovascular death (personal communication).

**Conclusion**

It emerges from the above that, apart from the classical renal risk factors and progression promoters, e.g. blood pressure, proteinuria, protein intake etc., smoking is a further hitherto neglected renal risk factor. In the future this fact must be taken into consideration in the management of patients with renal disease.

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**References**