There are numerous harmful substances found in tobacco and tobacco smoke. Nicotine is one of these substances that may be acquired through active and passive smoking. Associated with nicotine exposure is the incidence of occupational influences, passive smoking, nephrotoxicity, induced nephropathy and possible treatments.

This review aims to describe the influence of nicotine, smoking, smoke extracts and tobacco contaminants on renal function, with associated effects on cardiovascular function and various signal transduction pathways, by incorporating current references and expounding on previous reviews\textsuperscript{1-6}. A discussion and recommendation for denicotinising cigarettes and tobacco products are also presented.

**Nicotine - sources and health aspects**

The tobacco plant contains over 2,200 compounds of which nitrogenous compounds comprise more than 30 per cent\textsuperscript{7}. Torikai \textit{et al}\textsuperscript{8}
demonstrated that in burley tobacco leaves, there is a significantly higher content of pyridinic nitrogen than in bright or oriental tobacco leaves. The profiles of 29 known toxic compounds in tobacco smoke have been mentioned. Nicotine (3-{1-Methyl-2-pyrrolidinyl}pyridine; C_{10}H_{14}N_{2}; M_{r}=162.23) is one important alkaloid contained in tobacco leaves. Nicotine, however, is not the principle adverse constituent in combustion cigarette products. The primary commercial source of nicotine is by extraction from the dried leaves of the tobacco plant (Nicotinia tabaum and N. rustica). Smoking may affect people of any age, nicotine travelling rapidly in the blood stream and carbon monoxide binding to haemoglobin in red blood cells. In addition, the carcinogen benzo [a] pyrene binds to cells in the airways and major organs of smokers, and depresses immune function. Smoking results in an elevated incidence of chronic inflammation as a consequence of oxidative stress. Cigarette smoking increases the risk of developing numerous cancers including the lip, mouth, pharynx, oesophagus, pancreas, larynx, lungs, uterine cervix, urinary bladder and kidneys. Cigarette smokers are 2-4 times more likely to develop coronary heart disease than non-smokers. Contact with second hand or passive smoke exposes people to approximately 50 carcinogens resulting in an elevated risk of lung cancer and coronary heart disease, and an increased incidence of asthma, bronchitis and pneumonia in children. Exercise has been suggested as an intervention for smoking cessation.

**Nicotine consumption**

In man, nicotine is commonly consumed via smoking cigarettes, cigars or pipes. Nicotine may also enter the body via low tar Eclipse cigarettes, snuff, tobacco chewing, and pharmaceutical nicotine products like nicotine patches. Smokeless tobacco contains 28 carcinogenic agents and increases the risk of developing cancer in the mouth, as well as leading to nicotine addiction and dependence. The cigarette has been described as an efficient nicotine carriage device delivering an optimum dose of nicotine to the dependent brain. Ventilated cigarette filters dilute smoke with air and reduce standard yields of tar, nicotine and carbon monoxide. There is, however, no convincing evidence that changes in cigarette design have significantly reduced diseases caused by cigarettes. Nicotine replacement therapy can occur through products like the NiQuitin CQ transdermal patch; the Nicorette Microtab; the Nicorette inhalator; and the Nicotinell lozenge. These alternatives are safer than exposure to combusted tobacco which has numerous other constituents that are harmful to the body. Indeed, the risk of nicotine replacement therapy is very low. Other therapies promoting an increased smoking cessation rate with little effect on withdrawal symptoms, for example, nortriptyline (started at 25 mg 14 days before quit day, titrated to 75 mg/day as tolerated) combined with transdermal nicotine (21 mg/day) may represent an option for smokers in whom standard therapy has failed.

**Nicotine addiction and metabolism**

Nicotine has a dangerous effect on the body by modulating behaviour and dependence resulting in addiction and subsequent repeated exposure to toxins found in tobacco and tobacco smoke. Social aspects, peer pressure, stress, alcohol consumption, etc., are all behavioural factors that contribute towards addiction. The addictive liability and pharmacological effects of smoking are primarily mediated by the major tobacco alkaloid S- (-)-nicotine (nicotine). Nicotine is metabolized to S- (-)-nicotine Δ^1-5'-iminium ion by the genetically variable hepatic enzyme cytochrome P-450 2A6 (CYP2A6) and then to the pharmacologically less active derivative, S-cotinine (cotinine), by aldehyde oxidase.

**Cancers of the urinary tract**

Cigarette smoke and its metabolites cause cancers of the bladder and kidney resulting in the death of over 40 per cent of men in some countries of Eastern and Central Europe, and 17 per cent of women in the USA. Risk factors for renal cell
Carcinoma include cigarette smoking presumably accelerating the risk in a patient whose first-degree relative is suffering with kidney cancer, that is, an elevated odds ratio above 2.5, 95 per cent C.I. 1.04-5.90^28. Tobacco and cigarette use especially on a Western diet (high total fat; fried or broiled meats; low in fibre, vegetables and fruits) pose a high risk for renal cancer growth^29. Cigarette smoking is associated with elevated plasma carcinoembryonic antigen (CEA) levels among patients suffering from non-neoplastic diseases including chronic renal failure^1. Further studies have demonstrated that the prominent nicotine-related alkaloid β-nicotyrine present after smoking potently inhibits human CYP2A6^30. As CYP2A6 is involved in the metabolic activation of numerous carcinogens^31 reduction in this enzyme could potentially promote the development of renal carcinoma.

**Occupational exposure to cigarette smoke**

A recent report indicates the passing of a new federal bill in Germany to reduce exposure to environmental tobacco smoke in the workplace^32. Exposure to tobacco smoke at work increases the risk of urinary detection of nicotine and cotinine two-fold. Of concern, however, is the exposure of non-smokers to smoking family members at home. Serum cotinine concentration by occupation has been detailed^33. Mean serum cotinine levels ranged from 0.09 (farming, forestry and fishing jobs) to 0.22 ng/ml (operators, fabricators and labourer jobs). It is interesting to note that waiters had the highest cotinine output suggesting a high stress job. Such working conditions would presumably favour repeated smoking and further reinforce addictive behaviours.

**Heavy metal renal intoxication following smoking**

A recent study indicated that Lead (Pb)-linked glomerular dysfunction was observed in smokers, possibly due to more recent exposure to high levels of Pb, as reflected by 30-50 per cent higher serum cadmium (Cd) and Pb levels in smokers than non-smokers^34. Cd is a cumulative nephrotoxicant that is absorbed from food and cigarette smoking^35. Systemic Cd distribution occurs in animals whose lungs have been damaged through inhalation of products containing this heavy metal^16. This represents a major occupational hazard. Cd is a metal used in the zinc, copper and steel industries, and in the manufacture of electric batteries and solar cells^37. The authors suggest that chronic overexposure to Cd contributes towards the development of IgA mesangial glomerulonephritis^37. Presumably, cigarette smoking, which is a considerable source of Cd, is likely to intensify this condition. Smoking of 20 cigarettes per day results in inhalation of approximately 3.6-6.0 µg of Cd^38. The nephrotoxicity of Cd results in changes in proximal tubular function^38, characterized by an increased excretion of beta 2-microglobulin and giving rise to the classical tubular proteinuria and in a glomerular dysfunction evidenced by an increased excretion of high molecular weight proteins and increased levels of beta 2-microglobulin and creatinine in plasma, and giving rise to a glomerular type proteinuria^39,40.

**Passive smoking**

Exposure to passive smoke is clearly a health risk. This includes an enhanced exposure to carbon monoxide of a non-smoking visitor in a recreational environment and in the workplace^41. There is some indication of an elevated breast cancer risk associated with passive smoking exposure of 5 h or more per day at work (overall risk = 1.6)^42. Occupational exposure to tobacco smoke is damaging to children^43. In their questionnaire study on pupils aged 13-15 yr, smoking was found to occur at home (30.2%), at a friend’s place (29.3%), in public places (12.1%), at social events (10.4%), and at workplaces (1.5%). Group therapy, individual counselling, use of self-help materials, and nicotine replacement therapy have been described^44. Strong evidence suggested that interventions directed at individual smokers helped them to quit following advice from a health professional, individual and group counselling, and pharmacological treatment.
Nicotine induced nephropathies

Nephropathies are accelerated by nicotine with an increased incidence of microalbuminuria progressing to proteinuria, followed by type-1 diabetes mellitus induced renal failure. The risk for end stage renal disease (ESRD) was independent of age, ethnicity, income, blood pressure, diabetes mellitus, prior history of myocardial infarction, or serum cholesterol. Smoking vastly accelerates mortality in diabetic patients. The increased risk for macrovascular complications coronary heart disease (CHD), stroke, and peripheral vascular disease, is most pronounced in type 2 diabetic patients. The development of type 2 diabetes is another possible consequence of cigarette smoking besides the better known increased risk for cardiovascular disease. Smoking is harmful to albumin excretion because it increases the risk of microalbuminuria; shortens the interval between onset of diabetes and the start of albuminuria or proteinuria; accelerates the rate of progression from microalbuminuria to persistent proteinuria; and pathologically promotes the progression of diabetic nephropathy to ESRD.

Associated influence of nicotine on the nervous system

Renal injury induced by cigarette smoke condensate is reversed by renal denervation. Cigarette smoke-induced renal damage is due, at least in part, to activation of the sympathetic nervous system. In a study on rats exposed to long-term passive smoking for a short period of about 24 h after birth, the diameter of glomeruli in smokers was slightly smaller than in non-smokers (96.42 ± 7.15 vs 99.92 ± 5.56 µm, respectively). Associated elevations in nicotine-induced sympathetic nervous activity, would justify the increase in heart rate and arterial pressure mediated by systemic vasoconstriction in healthy non smokers, probably through alteration of a cyclic-GMP-dependent vasoactive mechanism. Additionally, alterations of normal sympathetic nervous activity may contribute to volume expansion (VE) in the nephron causing a significantly blunted diuresis and natriuresis.

Influence of nicotine on blood pressure

Chronic alterations in renal perfusion pressure and haemodynamics may be associated with cigarette smoke-induced cardiovascular and pulmonary diseases by modulating endothelin-1 mRNA expression. Smoking is an independent risk factor for renal function decline in patients with essential hypertension. Raised blood pressure compromised by atherosclerosis and reduced basal whole nitric oxide production potentially increases renal secretion of electrolytes. In a study where non-smokers were compared with smokers, impaired renal function resulted in a significant reduction in renal plasma flow. This would further compromise electrolyte-handling mechanisms in the nephron. Diabetics who smoke have elevated levels of fibrinogen and higher systolic blood pressures by comparison with non-smokers. This results in a higher incidence of myocardial infarctions and a reduced survival rate. Further complications have been shown in other studies. Smoking causes a significant increase in mean arterial pressure (MAP) (from baseline 92.8 ± 8.98 to 105 ± 7.78 mmHg) and heart rate (from 61.7 ± 7.52 to 86.4 ± 9.87 beats/min), accompanied by a significant increase in plasma arginine vasopressin (from 1.27 ± 0.72 to 19.9 ± 27.2 pg/ml) and epinephrine (from 37 ± 13 to 140 ± 129 pg/ml).

Effect of nicotine on blood vessels

Nicotine encourages renal vasoconstriction in healthy non smokers possibly through alteration of a cyclic-GMP-dependent vasoactive mechanism. During smoking, glomerular filtration rate (GFR) decreased in all but one volunteer (from 120 ± 17.7 to 102 ± 19.3 ml/min per 1.73 m²), accompanied by a significant decrease of filtration fraction (FF) (from 21.3 ± 4.24 to 17.4 ± 3.41%) and an increase in renovascular resistance (from 97.6 ± 27.2 to 108 ± 30.4 mmHg x min/ml per 1.73 m²). This suggests
nicotine-induced haemodynamic damage, with further alterations in the renal handling of fluid and electrolytes. Additionally, cigarette smoke-induced vascular damage predisposes patients to cardiac disease following renal transplantation\textsuperscript{57}. Cigarette smoking is also associated with augmented progression of nephropathies responsible for end-stage renal disease\textsuperscript{58,59} by its direct toxic effects on the vascular epithelium\textsuperscript{60}. Arteriolar hyalinosis has been detected in 23.5 per cent of non smokers and in 35.7 per cent of smokers (135 patients), showing a trend toward hyalinosis in chronic smokers\textsuperscript{61}. In patients with renal, especially glomerular disease, cigarette smoking exhibits a deleterious effect on the kidneys primarily through damage of small interlobular arteries\textsuperscript{61}.

**Lipid peroxidation**

Concurrent long term alcohol intake and cigarette smoking commonly leads to impairment of renal and hepatic function. Ethanol, nicotine, or a combination of ethanol plus nicotine significantly increases lipid peroxidation, respectively, in the liver, and decreased superoxide dismutase activity and increased catalase activity in the kidney\textsuperscript{62}. Cigarette smoking has a negative impact on plasma-circulating products of lipid peroxidation in haemodialysis (HD) patients\textsuperscript{63}. The lower blood levels of the glutathione (tGSH) and non-GSH free sulphhydryl compounds (non-GSH fSH) in HD patients who smoked suggest that these patients may be more susceptible to oxidative damage caused by smoking\textsuperscript{63}. Progressive kidney failure is associated with a gradual decrease of renal and non-renal elimination of nicotine\textsuperscript{64} further potentiating nephronic pathophysiology. Cigarette smoke is a common oxidant stress factor and may adversely affect the antioxidant capacity in humans and animals, to aggravate age related disorders\textsuperscript{65}. In this study, the baseline values of GSH in mice, and the ratio of GSH and oxidized GSH (GSSG) following air exposure were altered with age. The same values after exposure to cigarette smoke were changed markedly with advancing age. These results indicate that GSH metabolism may be impaired by chronic cigarette smoke exposure and that aged mice are more susceptible to cigarette smoke than young mice\textsuperscript{65}.

**Should nicotine be removed from combustion tobacco products?**

Behavioural manipulations to reduce exposure to inhalation of cigarette smoke are important and include a switch to denicotinised cigarettes\textsuperscript{66}. The authors demonstrated that switching to smoking denicotinised cigarettes for two weeks decreased the rewarding effects of the usual-brand test cigarettes. In order to re-enforce this smoking cessation, positive changes in behaviour through motivational counselling have been suggested\textsuperscript{67}. During treatment of nicotine addiction, one study found that there is a dose-response relationship between the number and duration of sessions and the quit rate\textsuperscript{68}. It was demonstrated that smokers must select a target quit day and stop smoking completely on that day as even a few cigarettes per day in the first fortnight resulted in relapse. The use of nicotine replacement products or bupropion improved success rates\textsuperscript{69}. Alternatively nicotine-free combustion cigarettes may help, although exposure to other combustibles would not be prevented.

**Conclusion**

Exposure to nicotine and combustible products from cigarette smoking is toxic to renal function. In particular, nicotine has an adverse effect on behaviour as it results in people becoming addicted. Patients are predisposed to urinary tract cancers. Further kidney damage can result from accumulation of heavy metals from tobacco. Associated with altered renal function is a direct effect on nervous innervation, blood pressure and blood vessels. Anti-smoking campaigns should be focused on achieving more success. For instance, banning smoking in public venues and at workplaces, will decrease the deleterious effects of long-term exposure to nicotine. Nicotine could also be removed from combustion tobacco products. Alternatively nicotine-replacement
therapies may be used. One should avoid smoking by inhalation either actively or passively.

References


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