EDITORIAL

Cadmium, Nicotine and Cigarettes: Any Hypertension Paradox?

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Tobacco smoke is said to be a complex mixture of many toxic chemicals deleterious to the cellular and tissue functions in the body. These include the polycyclic aromatic hydrocarbons (PAHs), aromatic amines and N-nitrosamines said to be carcinogenic (1). The World Health Organization (WHO) estimates an annual mortality of about 10 million smokers by year 2025 (2), with respiratory and cardiovascular diseases being the major causes. Active and passive (second hand) smoke exposures are reported to be associated with transient increases in heart rate and blood pressure, increased coronary vasoconstriction (3), haemodynamic stress, oxidant injury (4), neutrophil activation, enhanced thrombosis and increased fibrinogen and blood viscosity (5), dyslipidaemia, proteinuria, endothelial dysfunction and increased blood pressure (6), an observation very much under debate amongst researchers (7).

The cardiovascular risk effects through smoking have come from some such constituents as carbon monoxide, ethylbenzene, isopropylbenzene, trichloroethylene, phenol, oxidant gases, cadmium and nicotine (1). These chemicals have been implicated in damage to the kidneys as well as other vascular tissues.

A single cigarette smoke contains about 1000–3000 ppb of cadmium with 5.6E-06 cancer risk value [mg m^{-3}] (1, 8), and affects both active and passive smokers alike. As such, smoking is considered and accepted as a risk factor for development and progression of chronic to end-stage kidney disease and diabetic nephropathy, disease conditions leading to hypertension. Smoking is also reported to elicit an acute systemic adrenergic response (9).

Cadmium toxicity has been linked to several cardiovascular dysfunctions through its damage to the vascular endothelium, reduction in availability of NO (nitric oxide) and decrease in vascular smooth muscle cell viability (10, 11). The decrease in endothelial nitric oxide synthase (eNOS) protein levels also disrupts and interferes with signal pathways and receptor functions, further resulting in vascular dysfunctions. Cadmium is also reported to alter intracellular calcium transient mechanisms and lead to increased vasoconstriction, all leading to an increased blood pressure (11, 12). Cadmium toxicity and effects on tissue dysfunctions are predicted on its ability to disrupt genomic processes through DNA methylation (13) and increase in the reactive oxygen species (ROS). The increased oxidative stress occasioned by cadmium exposure is reported to also cause an increased production of low-density lipoprotein and end products of glycation (14, 15), further increasing inflammatory cascades and vascular damage. These increasing oxidative stresses in the vascular tissues are the major causes of arteriosclerosis.

Nicotine is reported to have anti-inflammatory and antioxidant properties with a capability to mop up free radicals (16-18), and is used to help subjects desirous of quitting smoking (19). Its actions are *via* the α-7 nicotinic acetylcholine receptors [α-7nAchR] (20). Its effects on vascular tissues are vasodilatory in nature through the induction of eNOS (21). Agarwal *et al* reported that long-term oral nicotine reduced proteinuria and renal inflammations and also preserved kidney functions (16). Some other researchers have reported negative potentials of nicotine to include increasing the addiction, as well as some of the pharmacological complications like cutaneous vasoconstriction (22), acceleration of nephropathies, increased renal failure due to microalbuminuria and proteinuria (23). Cooper further stated that nicotine increases lipid peroxidation and catalase activity, while decreasing the superoxide dismutase activity (23). Westman (24) and Najem *et al* (25) reported that nicotine could cause elevation of the heart rate and blood pressure. This may be through an inducement of the cFOS gene expression in areas of the brain essential in the regulation of cardiovascular functions (26), and activation of the sympathetic nervous system (27). Such activation can trigger a release of catecholamines, increased heart rate, coronary spasms and systemic blood pressure. Nicotine is also reported to promote glomerulosclerosis, mesangial proliferation and tubulointestitial fibrosis through production of extracellular matrix and mesangial cells (28) and cause a reduction of GFR (6), but effects on lipid profiles remain ambiguous (29).

Nicotine seems to have a dual effect: some usefulness and deleterious effects on tissue needs. That it is used in therapy for smoking cessations with success becomes even paradoxical with all the attendant reports of its deleterious effects. McRobbie and Hajek (30) explicitly stated that "none of the effects of nicotine has been shown to be pathognomonic". Smokeless and smoking tobacco have similar effects of transient elevations in blood pressure but

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smokeless tobacco shows a lower incidence of endothelial dysfunction, platelet activation, inflammatory and oxidant stress as seen with smoking tobacco (31). This gives the notion that smokeless tobacco is less deleterious than smoking tobacco (32). Many oxidizing chemicals like free radicals, PAHs, benzo(a)pyrene and 7,12 demethyl benz (a) anthracene, butadiene and oxides of nitrogen are inhaled during smoking; these are constituents of the tar and gas phases of cigarette smoke and are associated with depletion of endogenous levels of antioxidants (33) and accelerate atherosclerosis in experimental animals (31). Therefore, establishing the correct dose and route of administration of nicotine are key steps to be considered in reducing the likelihood of producing cardiovascular toxicities and adverse effects of other areas of the body.

So the paradox remains on the contribution of cadmium and nicotine, essential constituents of tobacco, on the cardiovascular function changes associated with smoking. There is much evidence linking cardiovascular diseases with smoking, but the exact mechanisms involved and its association with the various components remain ambiguous, as many researchers are not yet in agreement. Experimental studies on the pharmacokinetics and pharmacodynamics of these chemicals (cadmium and nicotine) can throw more light on possible interactions, synergy and combinational effects in the development and progression of cardiovascular diseases due to smoking.

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