

REVIEW

Smoking and hormones in health and endocrine disorders

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Abstract

Smoking has multiple effects on hormone secretion, some of which are associated with important clinical implications. These effects are mainly mediated by the pharmacological action of nicotine and also by toxins such as thiocyanate. Smoking affects pituitary, thyroid, adrenal, testicular and ovarian function, calcium metabolism and the action of insulin. The major salient clinical effects are the increased risk and severity of Graves' hyperthyroidism and ophthalmopathy, osteoporosis and reduced fertility. Smoking also contributes to the development of insulin resistance and hence type 2 diabetes mellitus. An important concern is also the effect of smoking on the foetus and young children. Passive transfer of thiocyanate can cause disturbance of thyroid size and function. Furthermore, maternal smoking causes increased catecholamine production, which may contribute to under perfusion of the foetoplacental unit.

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Introduction

The health consequences of cigarette smoking and of the use of other tobacco products are well known. They are an important cause of increased mortality and morbidity in developed countries and the prevalence is increasing in the developing world as well. Cardiovascular disease due to atherosclerosis is the major cause of death due to smoking. Cigarette smoking is an important predisposing factor for the development of chronic bronchitis and emphysema. The risk of cancer is also much greater in smokers than non-smokers, which is particularly true for lung cancer. Fertility problems are more likely in couples who smoke and maternal smoking in pregnancy is associated with intrauterine growth retardation.

Tobacco smoke contains numerous compounds, the important substances of medical significance being the carcinogens (such as polycyclic aromatic hydrocarbons), irritant substances, nicotine, carbon monoxide and other gases (1). Smoking has an affect on the various metabolic and biological processes in the body including secretion of hormones. These are mediated chiefly through behavioural and pharmacological actions of nicotine but also occur as a result of increases in the physical effects of stress on the body caused by smoking. In normal men, smoking causes an increase in heart rate and blood pressure as a result of constriction of blood vessels. It tends to increase the concentration of fatty acids in the blood

and also the liability of blood platelets to adhere to each other and to the walls of blood vessels. Nicotine also causes stimulation and sedation of the central nervous system depending upon the dose. Carbon monoxide in tobacco smoke has a higher affinity for haemoglobin, thereby reducing the oxygen-carrying capacity of the blood. The aim of this review is to describe the effects of smoking on the various hormones with its clinical consequences and to discuss the association of smoking with endocrine diseases.

Thyroid

Cigarette smoking has multiple effects on the thyroid gland. It has both stimulatory as well as inhibitory actions on thyroid function and is also a powerful risk factor for development of thyroid disease. Graves' disease, Graves' ophthalmopathy and thyroid hormone abnormalities have all been linked to smoking.

In normal adults, smoking has either a weak stimulatory or no effect on thyroid function and size. Small increases in thyroid hormones, mainly serum triiodothyronine and thyroglobulin concentrations may occur (2). The mechanism for this is unclear but nicotine-induced sympathetic activation could account for the increased thyroid hormone secretion. Though TSH levels have been reported to be lower in smokers in a few studies (3–5), others have not found this effect (6). Thus in smokers with no symptoms or signs of thyroid over or under activity, the mild

elevation of thyroid hormones could represent a smoking effect and not intrinsic thyroid disease.

Parental smoking also has an effect on thyroid function in infants. Infants of parents who smoke have higher cord concentrations of serum thyroglobulin and thiocyanate at birth and at 1 year of age than infants of non-smoking parents (7). Significantly, in the same study, cord serum thyroglobulin concentrations were increased in infants whose fathers, but not mothers, smoked, suggesting a passive transfer of components of tobacco smoking (likely to be thiocyanate) stimulating thyroglobulin secretion. No differences were observed in thyroid hormone levels. However, others have found an increase in serum thyroxine levels and a decrease in TSH levels in infants delivered at term by smoking mothers (8). Smoking during pregnancy has also been reported to cause neonatal thyroid enlargement (9). As such, the weak stimulatory effects of smoking observed in normal adults are also seen in infants of smoking parents.

There are several mechanisms by which smoking affects thyroid hormone levels. Tobacco smoke contains several toxins such as thiocyanate and 2,3-hydroxypyridine. Thiocyanate has been shown to be a potential goitrogen (10). Thiocyanate, which has a half-life of more than 6 days, inhibits iodide transport and organification as well as increasing the efflux of iodide from the gland. In the presence of iodine deficiency thiocyanate can cause goitre. 2,3-Hydroxypyridine, on the other hand, inhibits thyroxine deiodination by limiting iodothyronine deiodinase activity (11). This effect may slightly but temporarily elevate serum thyroxine levels as a result of its deiodinase-altering activity prior to decreasing the levels (5).

With regards to disease states, there is enough evidence to suggest that cigarette smoking is a risk factor for Graves' hyperthyroidism and especially Graves' ophthalmopathy. Graves' ophthalmopathy is strongly associated with smoking (12–17) – the more severe the eye disease the stronger is the association. The number of cigarettes smoked per day is a significant independent risk factor for the incidence of proptosis and diplopia. Smoking also increases the risk for progression of ophthalmopathy after radioiodine therapy and decreases the efficacy of orbital radiation therapy and glucocorticoid treatment (18). The response to treatment in patients with ophthalmopathy is delayed and markedly poorer in smokers (19). The mechanisms by which smoking affects Graves' ophthalmopathy are not fully understood. Probable explanations include the fact that smoking may aggravate tissue hypoxia and exert important immunomodulatory effects (20). Extraocular muscle fibroblasts respond differently from dermal fibroblasts to stimulation by cytokines and also by hypoxia, thus possibly contributing to the effect of smoking on eye disease (21). Graves' disease without ophthalmopathy is also associated with smoking though this correlation is weaker (17, 22).

However, smoking has been found to increase the relapse rates in males with Graves' disease after stoppage of anti-thyroid medication (23), though the presence of goitre and ophthalmopathy also reduced the chances of remission. At the other end of the disease spectrum, a study in women with hypothyroidism showed that those subjects with subclinical hypothyroidism who were smokers had higher serum TSH concentrations and a higher serum ratio of triiodothyronine to free thyroxine than non-smokers. However, in the same study, in patients with overt hypothyroidism, smokers and non-smokers had similar thyroid hormone concentrations but smokers had more severe symptoms and signs (24). Thus smoking probably reduces thyroid secretion in patients with subclinical hypothyroidism and exacerbates the peripheral effects of thyroid deficiency in overt hypothyroidism (2). Nystrom *et al.* (25) also reported an association between smoking and subsequent development of hypothyroidism at the time of initial screening but no association was seen between smoking habits and hypothyroidism at the end of the 12-year follow-up. A meta-analysis has suggested that Hashimoto's thyroiditis and postpartum thyroid dysfunction are associated with smoking but the association with hypothyroidism was not statistically significant (17). There is evidence to suggest that in Hashimoto's thyroiditis smoking may contribute to the development of hypothyroidism through an increase in thiocyanate levels (26).

Another common presentation of thyroid disorder is goitre. Goitre can occur as a normal feature of puberty and pregnancy but can also be caused by a range of factors that include iodine deficiency and autoimmune thyroiditis. The prevalence of non-toxic goitre is higher in smokers than non-smokers and this has a significant bias to women than men (3, 4, 17, 27, 28). Thiocyanate is goitrogenic which is possibly responsible for the increased prevalence of non-toxic goitre. Though Ericsson *et al.* (4) found a higher prevalence of toxic diffuse goitre in smoking women, a meta-analysis showed that smoking was not associated with toxic nodular goitre (17). As a diffuse goitre is often seen in patients with Graves' disease, an increase in sympathetic activity in smokers may promote the development of thyrotoxicosis in these predisposed individuals.

In sharp contrast, cigarette smoking has been found to be negatively associated with thyroid cancer (29–33). This could be partly due to the greater occurrence of the disease in women. However, even in women there is a reduced risk for all histological groups of thyroid cancer. In men, though Kreiger & Parkes (29) reported a reduced risk of thyroid neoplasia with smoking, others found no effect (33). The protective effect of smoking could be due to a number of different mechanisms that reduce thyroid cell proliferation including effects on thyroid-stimulating hormone and oestrogen metabolism. As mentioned earlier, a few studies have shown that cigarette smoking lowers TSH levels and

this might protect against thyroid cancer though not all studies have supported this effect. Oestrogen metabolism may also have a role in the pathogenesis of thyroid cancer as an increased risk is seen in women with early first childbirth and with a history of artificial menopause (30). Smoking has been shown to have an anti-oestrogenic effect (34) and thus could protect against development of thyroid carcinoma.

Pituitary hormones

Cigarette smoking stimulates the release of several anterior and posterior pituitary hormones. Smoking acutely increases the plasma levels of prolactin, adrenocorticotrophin (ACTH), growth hormone (GH) and arginine vasopressin (AVP) without significant changes in TSH, luteinizing hormone (LH) and follicle-stimulating hormone (FSH) (35–38). These effects are directly proportional to the nicotine content of cigarettes, with greater hormonal responses observed in high content cigarettes (37). Though all these studies were done in males, similar acute hormonal changes with smoking in women would be expected. There are four potential mechanisms which may cause these effects. First, nausea induced by smoking may produce an increase in cortisol, GH, prolactin and antidiuretic hormones as similar effects are seen to accompany nausea and vomiting during rapid rotation (35). The neurochemical events that occur with nausea are co-ordinated by the brain stem emetic centre and nicotine is known to stimulate the emetic centre and could thus contribute to smoking-induced nausea. Another possible mechanism is via nicotine-stimulated cyclic AMP production as demonstrated in rats (36). Stress *per se* could also cause the release of these hormones. A direct effect of nicotine or neurotransmitters released by nicotine, acting on the anterior pituitary or hypothalamus, could be another possibility.

In chronic smokers, however, inhibition of prolactin secretion occurs. The inhibitory effects of chronic nicotine exposure on prolactin secretion are probably produced via an activation of nicotinic receptors of the tuberoinfundibular dopamine neurones releasing dopamine as a prolactin-inhibitory factor (39). Besides this, in a study using the GH3 rat pituitary cell line, nicotine was shown to downregulate prolactin gene expression (40). Baseline prolactin levels are thus lower in chronic smokers than non-smokers (41, 42). This may contribute to the reduced fertility in smokers. Importantly, pregnant women who smoke have lower prolactin levels towards the end of pregnancy (43). Furthermore, significantly lower prolactin levels are found to occur in breast-feeding smokers, though suckling-induced acute increases in serum prolactin and oxytocin-linked neurophysin were not influenced by smoking (44). In this study, smokers were found to wean their babies significantly earlier than non-smokers. Thus smoking women

may have a shorter period of lactation due to the lower prolactin levels.

GH levels are also acutely increased by smoking though the response is less in older subjects (45). Insulin-like growth factor-I (IGF-I) levels, however, show a downward trend with increasing smoking especially in men (46). As the secretion of IGF-I is largely dependent on GH, long-term smoking may lead to a downregulation of GH release. Smoking probably influences IGF-I concentrations via central hypothalamic pathways. As GH substitution treatment in GH-deficient adults is titrated to achieve normal IGF-I concentrations, the smoking status would have to be taken into account when determining normal IGF-I concentrations.

Gonadotrophin concentrations are not largely affected acutely by smoking. However, in habitual smokers both active and passive smoking is associated with elevated FSH concentrations in perimenopausal women (47, 48). This results in a shorter duration of the transitional period to menopause. In men, the levels of gonadotrophins have been reported to be unchanged (49) though others have found increased (41) or decreased LH (50) levels in smokers.

Smoking acutely increases vasopressin levels (35, 51, 52). This could account for the acute hypertensive responses after smoking. As nicotine given intravenously does not affect vasopressin levels, an airway-specific mechanism, through irritation of the sensory nerve terminals in the respiratory epithelium by cigarette smoke, could be responsible for vasopressin release (39).

Maternal smoking also causes disturbances in the endocrine equilibrium of the foetus. Increased levels of prolactin, GH and IGF-I are observed which are more pronounced between 30 and 37 weeks of gestation than at term (53). The most plausible explanation of hormonal abnormalities in neonates of smoking mothers is foetal distress due to underperfusion of the foetoplacental unit and acute decreases of placental blood flow associated with smoking. However, a direct effect of nicotine is another possibility. The high hormone levels observed in the above study persisted for at least the first 3 days of life likely due to the additional stress caused by adaptation to the extrauterine environment.

Adrenal hormones

Cigarette smoking alters the levels of endogenous steroid hormones. As discussed earlier, an acute rise in circulating cortisol is observed after smoking. Even in chronic smokers salivary free cortisol secretion has been shown to be enhanced compared with non-smokers (54) though Yeh & Barbieri (55) did not find abnormally elevated levels of 24-h urinary free cortisol in chronic smokers. Interestingly, cortisol levels drop significantly in people who give up smoking especially during the early withdrawal process (56). Some of the mechanisms for the acute rise in cortisol and ACTH

have already been mentioned. Nicotine is also known to increase vasopressin which may cause increased ACTH and cortisol secretion (57).

The renin-angiotensin system is also affected by smoking. The acute response to smoking is an increase in systolic and diastolic pressure and tachycardia. Smoking has been shown to acutely increase plasma aldosterone and angiotensin converting enzyme activity in hypertensive (58) and normotensive (59) patients. However, no acute change in renin activity was observed. These effects could be due to the effect of ACTH on aldosterone, secondary to nicotine and also the adrenergic response seen after acute inhalation. On the other hand, chronic smoking stimulates plasma renin activity (60, 61) and raises plasma aldosterone levels. This could account for the enhanced vasoconstrictive reactivity of the arteries in chronic smokers.

Smoking also has effects on adrenal androgen secretion. Higher levels of androstenedione and dehydroepiandrosterone sulfate (DHEAS) are found in smokers (62–65). ACTH-stimulated androstenedione, 17-hydroxyprogesterone and dehydroepiandrosterone (DHEA) levels are reported to be higher in male smokers (66) though in another study the response to ACTH was found to be similar in postmenopausal smokers and non-smokers (62). The increased secretion of adrenal androgens could be caused by the inhibition of either 21 or 11 β -hydroxylase in the adrenal cortex. Elevated adrenal androgens may also contribute to insulin resistance reported in smokers as well as an increased risk of osteoporosis in elderly postmenopausal smokers.

Stimulation of the adrenal medulla occurs in smokers and is caused by nicotine-stimulated catecholamine release. Plasma adrenaline and noradrenaline levels rise after smoking (67–69). In elderly smokers, plasma noradrenaline concentrations have been found to be significantly elevated as compared with young smokers and non-smokers (70). Urinary excretion of catecholamines is also increased with smoking (71, 72). These effects result in an increase in heart rate and blood pressure. In hypertensive patients, total plasma catecholamines have been reported to rise 10 min after smoking, implying that smoking should be avoided prior to blood pressure measurements (58). Hypertensive subjects in fact exhibit the most exaggerated rise in urinary catecholamines and cardiovascular responses to smoking (71). Maternal smoking also causes an elevation of catecholamines and metabolites in the amniotic fluid, suggesting foetal adrenergic activation as a result of foetal hypoxia and/or by a direct effect of nicotine on the foetal adrenergic system (73).

Sex hormones

Cigarette smoking has major effects on the reproductive potential of humans. It has an anti-oestrogenic effect in women (34, 74, 75). This is probably due to changes

in hepatic oestrogen metabolism induced by smoking. Smoking has a powerful effect on the 2-hydroxylation pathway of oestradiol metabolism leading to increased production of 2-hydroxyestrogens (76). These compounds have minimal oestrogenic activity and are rapidly cleared from the circulation. Furthermore, in the circulation oestrogens bind avidly to sex hormone binding globulin (SHBG) (38%), loosely to albumin (60%) and the remainder is the free unbound fraction. In smokers, concentrations of SHBG are higher and lower concentrations of biologically active oestrogens are thus seen (77, 78). Animal data have also demonstrated a direct toxic effect of cigarette smoke on ovarian follicles (75).

Some normal oestrogen-dependent physiological processes such as the menstrual cycle are thus affected. Women who smoke have significantly more variable segment and menses length than non-smokers, with heavy smokers (≥ 20 cigarettes per day) running a risk of shorter segment length than non-smokers due almost entirely to the shortening of the follicular phase (79). The likelihood of irregular cycles increases with the number of cigarettes smoked (80). This leads to an increased risk of anovulation which becomes greater with the degree of smoking. These effects decrease fertility in women as well as reduce the age of menopause. Menopausal symptoms such as hot flushes are experienced more commonly among smokers (81). Some earlier studies, however, have found no significant differences in length of follicular or luteal phases of the menstrual cycle in smokers and non-smokers though the number of subjects studied was much smaller (82).

The efficacy of the oral contraceptive pill could be affected by smoking. Rosenberg *et al.* (83) showed that smokers were 47% more likely to have spotting or bleeding than non-smokers over six cycles of oral contraceptive use. Though women who have spotting and bleeding are more likely to discontinue the contraceptive pill placing them at increased risk of unintended pregnancy, the anti-oestrogenic effect of smoking may also impair the efficacy of the oral contraceptive pill.

Smoking also results in reduction in bone mineral density, making osteoporosis more common among female smokers. Though various mechanisms for this effect are described later in this review, part of the deleterious effect of smoking on bone is mediated through its oestrogen-lowering effect. It is important to take this into account when hormone replacement therapy (HRT) is considered for prevention of postmenopausal bone loss and osteoporotic fractures. The therapeutic efficacy of oral HRT, prescribed in conventional doses, is reduced in smokers (34, 84). This occurs as a result of increased hepatic clearance, as described previously, and is seen with oral preparations only. Thus smoking can counteract the protective effect of oral HRT on bone. Increasing the dose of oral oestrogen is not recommended as it results in the production

of toxic oestrogen conjugates, such as catechol oestrogens and 16 α -hydroxyoestrone, which have been implicated in breast cancer (34). As transdermal administration of oestradiol bypasses the liver and enables a lower dosage of oestrogen to be used, this route should be considered in women who continue to smoke despite all warnings (84). The parenteral route of HRT is another option.

Owing to its anti-oestrogenic action, certain diseases that depend on oestrogen for growth and development tend to be less common among smokers. The development of endometrial cancer is related to oestrogen levels and a lower prevalence of this cancer is seen among women who smoke (75, 85–87). Similarly, hyperemesis gravidarum, uterine fibroids and endometriosis are common disorders in young women and are oestrogen dependent. Again smokers have a reduced risk of developing these conditions (75). Though breast tissue is oestrogen responsive, the association between smoking and breast cancer is less well-defined (75, 88). In fact the inconsistent findings between smoking and breast cancer risk can be explained by the genetic susceptibility to carcinogens found in cigarette smoke and not the anti-oestrogenic effect (89). Ambrosone and coworkers (89) found that N-acetyltransferase 2 genetic polymorphism plays an important role in breast cancer risk.

In males, the effect of smoking on androgen levels is important, given the recent interest in the association between low androgen levels and the metabolic syndrome, and coronary heart disease (90). Various studies examining the effects of smoking on serum testosterone levels have reported conflicting findings largely due to difficulties in the hormonal assays. Testosterone has a circadian rhythm with levels peaking between 0600 and 0800 h and reaching a nadir between 1800 and 2000 h. A significant proportion of the circulating total testosterone is inactive as it is tightly bound to SHBG (65–80%), whereas the biologically active fraction circulates either free (1–3%) in circulation or loosely bound to albumin (20–40%). The free plus the albumin-bound testosterone is called the bioavailable testosterone. Thus levels of total testosterone can be affected by changes in the levels of SHBG and other plasma proteins. Significantly increased (41, 91–95), decreased (96, 97) and unchanged levels of total testosterone (64, 98, 99) in male smokers have been reported in various studies. Free testosterone levels have also been found to be higher among smokers (41, 91, 92, 94, 95). However, SHBG levels have been measured only in three studies (92, 93, 95) and are reported to be higher amongst smokers. No significant differences in the levels of bioavailable testosterone have been demonstrated between smokers and non-smokers (92, 93). English and colleagues (92) demonstrated that the increase in total testosterone observed in smokers is due to the raised SHBG levels. They also reported that SHBG levels and not testosterone

correlated with serum nicotine levels, a measure of cigarette smoking. However, Svartberg *et al.* (95) found a positive association between testosterone and smoking even after adjusting for SHBG though other plasma proteins were not taken into account. It would seem likely that the effects of smoking on testosterone levels are due to changes in plasma-binding capacity rather than a direct effect of nicotine on androgens.

Insulin resistance

Smoking may contribute to the development of insulin resistance, which is associated with an increased risk of cardiovascular disease. The effects of acute smoking result in significantly impaired glucose tolerance and hyperinsulinaemia in chronic smokers (100). Similarly, Attvall *et al.* (101) demonstrated that smoking acutely impairs insulin action due to lower peripheral glucose uptake. Cross-sectional studies have also shown hyperinsulinaemia and increased insulin resistance in smokers as compared with non-smoking controls (102). Importantly, an improvement in insulin sensitivity and increase in high-density lipoprotein cholesterol occurs after cessation of smoking (103). Even though smoking is associated with insulin resistance, a significant effect on HbA1c in type 2 diabetic subjects has not been reported (104). In type 1 diabetic subjects, insulin requirements have also been found to be either similar (105) or increased (106) in smokers.

The reduced insulin sensitivity seen in smokers could be due to the increase in counter-regulatory hormones such as GH, cortisol and catecholamines which all raise blood glucose levels. Increased glucagon levels have also been shown after acute smoking in type 1 diabetic men though substantial changes in insulin sensitivity were not observed in these patients despite the rise in counter-regulatory hormones (107). Others have shown that smoking in patients with insulin-dependent diabetes not only elicits higher GH, AVP and cortisol responses than in normal subjects but also enhances the counter-regulatory responses to insulin-induced hypoglycaemia (108). These effects probably play a role in the pathogenesis of diabetic complications as increased cortisol and AVP cause an increase in blood pressure and thus their enhanced secretion in smokers might contribute to cardiovascular, cerebrovascular and renal diseases. Sonksen *et al.* (109) have also suggested that hypersecretion of GH could be linked to the development of diabetic microangiopathy.

Parathyroid hormone (PTH) and bone

Smoking is implicated as a risk factor for osteoporosis and therefore increased susceptibility for fractures. It has a significant effect on calcium and vitamin D metabolism. This has been studied mainly in peri- and

postmenopausal women. Calcium absorption is lower in smokers as compared with non-smokers. This is attributed to the lower PTH and serum calcitriol levels seen in smokers (110–112). The impairment of calcium absorption results in accelerated bone loss as well as decreased usefulness of dietary calcium supplements. However, in another study, even though serum 25-hydroxyvitamin D levels and calcium absorption was lower in both light and heavy smokers, PTH levels were higher in heavy smokers (113). Thus the adverse effects of smoking on the skeleton could be due to significant changes in the vitamin D–PTH system seen among smokers.

Various other mechanisms for the increased risk of osteoporosis in women have been described. Postmenopausal chronic smokers have significant elevated levels of cortisol as compared with non-smokers (114) and the hypercortisolism may increase the risk of osteoporosis. Smoking has also been shown previously to increase the levels of adrenal androgens, namely androstenedione and DHEAS, as well as to have an anti-oestrogenic effect which could contribute to the lower bone mineral density. Furthermore, it has been demonstrated that polycyclic aromatic hydrocarbons, present in cigarette smoke, cause bone loss in an ovariectomized rat model (115).

Even in males, smokers have a lower bone mineral density as compared with non-smokers (116). The reasons for this are not known, though the direct toxic effect of environmental toxins, present in cigarette smoke, on bone seems likely.

Conclusion

Smoking is an important modifier of hormones and a detailed smoking history is essential when assessing patients with endocrine disorders. The hormonal responses to smoking are responsible for the increased prevalence of several diseases in smokers. Graves' disease and particularly Graves' ophthalmopathy are strongly associated with smoking. Autoimmune thyroiditis and small goiters are also more commonly seen in smokers. Similarly, osteoporosis is linked to smoking through its effects on various hormones, in particular the anti-oestrogenic effect in women, which causes fertility problems and premature menopause in smokers as well. Insulin resistance is also more common in smokers and may contribute to the increased incidence of cardiovascular disease. More pronounced responses are seen in heavy smokers as compared with light smokers reflecting the direct toxicogenic effect of cigarette smoke. Maternal smoking affects the infants in a similar way to adults. It is also possible that passive smoking could also affect the growth of young children through decrease in GH, as seen in chronic smokers. The rewards of giving up smoking are thus both immediate and substantial.

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