

Review**Influence of cigarette smoking on thyroid function, goiter formation and autoimmune thyroid disorders**

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Both smoking and thyroid dysfunction are frequent in the general population. Many studies have shown that cigarette smoking interferes with thyroid function and with the evolution of thyroid pathology (e.g. goiter formation and thyroid cancer development). Some studies have also suggested a significant correlation of Graves' hyperthyroidism and Graves' ophthalmopathy with the severity of smoking. In addition, cigarette smoking may reduce the effectiveness of some therapeutic modalities, such as orbital radiotherapy or high-dose systemic glucocorticoid administration for severe thyroid eye disease. Tobacco smoking seems to induce similar changes in thyroid function in the adult and the fetus. This review article discusses the effect of cigarette smoking on thyroid function and morphology as well as on thyroid autoimmunity.

Key Words: thyroid function, goiter, thyroid cancer, Graves' disease, Graves' ophthalmopathy, autoimmune thyroid disorders, cigarette smoking

INTRODUCTION

Cigarette smoking has multiple effects on thyroid function and thyroid volume. These include minor and probably physiologically unimportant alterations in thyroid hormones¹⁻¹⁰ and thyrotropin concentrations¹⁻⁹, central (thyroid) and peripheral antithyroid action^{11,12}, thyroid gland stimulating or goitrogenic action^{1,2,4,13}, carcinogenesis lowering properties^{14,23} and also actions that increase susceptibility to Graves' disease^{24,25} and especially the incidence and clinical severity of thyroid associated ophthalmopathy²⁶. Finally, it seems that parental smoking may have deleterious effects on fetal thyroid secre-

tion and on thyroid function of some of these infants at one year of age^{27,28}. How smoking might affect thyroid economy is not completely understood. For the goitrogenic effect of smoking, thiocyanate has been implicated²⁹. However, other smoke products might have central or peripheral antithyroid actions, thyrotropin lowering activities or immunological effects, although it is not clear whether or not these latter actions play an important role in the pathogenesis of smoking related autoimmune disorders^{3,7,30,31}.

This article reviews current aspects of the role of cigarette smoking in thyroid function, goiter formation, the risk of thyroid cancer development and the incidence and severity of different autoimmune thyroid disorders.

SMOKING AND THYROID FUNCTION

Cigarette smoking has multiple, minor effects on thyroid function. Serum thyroxine (T4) levels remain un-

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changed¹⁻⁶ or are slightly elevated^{7,8}, while serum triiodothyronine (T3) levels may be increased²⁻⁴ or unchanged^{2,5-8}. Sepkovic et al⁹ found reduced serum T3 and T4 levels in heavy smokers. Of course, terms like increase or decrease do not necessarily indicate abnormal levels. In most of the above studies, the total values of thyroid hormones were determined. In some, however, free thyroid hormone levels were also analyzed, (although indirectly taking into account T3 resin uptake), and no difference with smoking habits was detected^{2,6,7,9}. Reverse T3 (rT3) was found to be reduced in smokers^{1,10}, while in two other studies increased levels of rT3 were associated with increased levels of T4 and unaltered levels of T3^{7,8}. Finally, Hegedus et al in two analogous studies found no differences in total T3, T4 and free T3 levels^{2,6}.

Thyrotropin stimulating hormone (TSH) levels were found to be decreased^{2,5-8} or unaltered^{1,3,4,9}. Muller et al.¹¹ however, found that among women with subclinical hypothyroidism, smokers had higher serum TSH levels, higher serum ratio of T3 to free T4, and also higher cholesterol and low-density lipoprotein cholesterol concentrations than non smokers¹¹. In contrast, patients with overt hypothyroidism either smokers or non-smokers, had similar serum TSH and thyroid hormone levels¹¹. These results do not indicate that smoking causes hypothyroidism, but that it may increase the severity of the effects of hypothyroidism¹². These variable results may be due to the fact that the various studies are not directly comparable. Although they were conducted in smokers and non-smokers, there were significant differences in age, sex, body weight, cigarette smoking habits, time of abstinence from smoking, previous thyroid function status, presence of thyroid autoimmunity and finally iodide status, factors known to affect the thyroid hormone levels.

In regard to thyroglobulin (Tg) levels, Christensen et al¹ found that smokers had significantly higher levels of serum Tg in comparison to non-smokers or ex-smokers. Hegedus et al² found the same results among smokers who were compared with individuals who had never smoked. They also found that Tg was positively correlated to the volume of the thyroid gland, with a higher correlation in smokers^{1,2}. However, even if the goitrous subjects were excluded, in this study serum Tg levels remained higher among smokers, indicating that smoking has an independent thyroid stimulating effect^{1,2}.

An interesting issue is the mechanism(s) by which cigarette smoking affects thyroid function. Thiocyanate (SCN⁻), a perchlorate like goitrogen, acts by preventing iodine and no difference with smoking habits were de-

tected accumulation (trapping) by the thyroid. It is generated from cigarette smoke as a detoxifying product of cyanide. The levels of the SCN⁻ in the blood are related to the amount of cigarette smoke inhalation³. SCN⁻ competitively inhibits iodide uptake and hormone synthesis and increases iodide efflux from the thyroid cells³⁰. This competitive inhibition of iodide transport may be important for understanding the action of SCN⁻ in vivo. Iodine deficiency may enhance the antithyroid actions of SCN⁻ and iodide excess may diminish the effect^{2,3,4}.

Although nicotine in cigarette smoking does not influence iodide turnover³⁰, it might cause sympathetic activation, which could increase thyroid secretion^{7,32}. Alternatively, nicotine or other component(s) of tobacco smoking, such as benzpyrene, may have direct thyroid-stimulatory actions or stimulating effects on hepatic oxidative metabolism, which in turn may stimulate hepatic conversion of T4 to T3³¹.

SMOKING AND GOITER FORMATION

It is well known that many factors are involved in the regulation of thyroid volume. TSH levels, iodine concentration, the presence of thyroid autoimmunity and several goitrogens are generally accepted factors but others, such as sex, age, body weight or personal habits (e.g. cigarette smoking, alcohol abuse) are controversial in regard to their effect on thyroid volume.

As far as the goitrogenic effect of cigarette smoking is concerned, Christensen et al¹ found an increased frequency of mainly multinodular goiter among middle-aged heavy female smokers in comparison with ex-smokers, but not between smokers and people who had never smoked. Similar results were reported by Lio et al⁴ who demonstrated a higher frequency of multinodular goiter among heavy smokers. Ericsson et al¹³ also found increased incidence of goiter, either diffuse or multinodular. The latter was more common in the elderly. Hegedus et al² using precise and accurate ultrasonic techniques³⁴ showed that median thyroid gland volume was increased in smokers of both sexes by 73%. Thyroid volume per body weight was also increased by 56% in smokers. Even when subjects with clinically detectable goiter were excluded, a significantly higher thyroid volume was found in those who were smokers². On the other hand Petersen et al⁵ found no association between smoking and goiter frequency or differences in thyroid volume between smokers and non-smokers. Berghout et al³⁵ failed to detect any correlation between thyroid volume and daily tobacco consumption (ranging from 5 to 15 cigarettes).

In two more recent studies from the Netherlands and Italy, no difference was found in the smoking habits of patients with non-toxic goiter and those of healthy controls^{24,36}. The above discrepancies are probably related to differences in the number of people examined, the age and sex of the study populations, the number of cigarettes consumed daily and the years of smoking, regional variations in dietary iodine intake, as well as variations in the methods used to assess thyroid size³² and even more, in the definition of goiter per se³⁷. It is well known, for example, that differences exist when thyroid size is measured by palpation in comparison to the ultrasonic method^{37,38}.

The goitrogenic action of smoking may be related to the goitrogenic effect of SCN- and probably other by products of smoke. The variation in the prevalence of goiter between different areas has been shown to be related to the level of urinary SCN- excretion³⁹. Serum SCN- levels are elevated in cigarette smokers and have been used as a reliable indicator of smoking habits²⁹. However, SCN-, which acts mainly by preventing iodine trapping, may not be a very important goitrogenic cofactor in iodine sufficient areas³⁷.

EFFECTS OF SMOKING ON THE RISK OF THYROID CANCER

Relatively little is known about the pathogenesis and aetiology of thyroid cancer beyond its association with radiation exposure and some preexisting thyroid diseases, including endemic goiter, sporadic goiter, lymphocytic thyroiditis and Graves' disease⁴⁰. During the last two decades, several studies have reported a reduced risk of thyroid cancer, mainly in women, albeit not always statistically significant, in association, with cigarette smoking¹⁴⁻²¹. However, only a few studies have addressed the effect of smoking on thyroid tumor in men^{16,22}. Kreiger and Parkers recently explored the association of cigarette smoking with thyroid cancer in both sexes in a case-control study²³. Reduced risk was observed for ever/never cigarette smokers for both sexes with an odds ratio of 0.71 for females (95% confidence interval (CI) = 0.60-0.83) and 0.77 (95% CI=0.58-1.02) for males. Dose-response effects were also observed in association with duration, quantity of cigarettes smoked and pack-years of exposure. There was no reduction in the protective effect associated with the age smoking was started or years since smoking was stopped. There was also evidence of reduced risk for all histological subgroups. Other investigators found similar although not always significant results in studies including only women^{14-16,20,21}, except in two stud-

ies which included men^{16,19}. Rossing et al²¹ reported that a history of ever having smoked more than 100 cigarettes was associated with a reduced risk of thyroid cancer (odds ratio 0.7, 95% CI=0.5-0.9). This reduction in risk was most evident in current smokers (odds ratio 0.5, 95% CI=0.4-0.7). Hallquist et al²² reported that both women who were previously smokers as well as current smokers had significantly decreased risks with odds ratio of 0.5 (95% CI=0.2-0.96) and 0.6 (95% CI=0.3-0.96) respectively. Galanti et al²⁰ reported a lower risk among young smokers, but no dose-response associated with the number of cigarettes or the number of years smoked. In contrast to the above mentioned studies, in a case-control study of 100 histologically verified thyroid cancer patients of both sexes and 100 matched controls, Sokic et al⁴¹ found no reduced risk of thyroid cancer in cigarette smokers.

Given that thyroid cancer occurs more frequently in women than in men, hormonal factors may also be involved in its pathogenesis. The mechanism (s) by which cigarette smoking may be protective for thyroid cancer is probably by lowering the endogenous levels of TSH [1, 8, 13, 42]. It has been suggested that increased levels of TSH⁴³ or elevated levels of other thyroid stimulators, as occurs during pregnancy, are associated with an increased risk of thyroid cancer¹⁵. Female preponderance of thyroid cancer has led to the hypothesis that estrogen metabolism may play a role in its pathogenesis. Indeed, it has been suggested by some studies that smoking may have an anti-estrogen effect⁴⁴. However there is no evidence that smoking has similar effect(s) on androgen metabolism⁴⁵.

THYROID AUTOIMMUNE DISORDERS IN CIGARETTE SMOKERS

a. Graves' disease

Graves' disease and Hashimoto's thyroiditis are the two main forms of so-called autoimmune thyroid disease (AITD). AITD is considered a polygenic, multifactorial disease which is characterized by activation of the immune system as a result of interactions between genetic predisposition and environmental factors⁴⁶. The latter includes iodine intake⁴⁷, seasonability, pollutants⁴⁸ infections⁴⁹ and stressful life events⁵⁰⁻⁵².

Cigarette smoking is an additional environmental factor which increases the risk for Graves' disease^{24,25}. The interrelationship of Graves' disease and smoking has been detected in numerous studies. The mean prevalence of smokers in a European population of 709 patients with

Graves' disease without relevant thyroid ophthalmopathy, extracted from seven studies, was 41% (22-56%)^{25,53}. The percentage of smokers among 167 patients with Graves' disease without ophthalmopathy was 48%, whereas the prevalence of smoking was 30% in patients with other thyroid disorders such as non-toxic nodular goiter, toxic nodular goiter and Hashimoto's thyroiditis³⁶. Similar results were found in two other case-control studies^{24,54}. The prevalence of smokers was 56% and 41% respectively in patients with Graves' disease and 41% and 30% in the control groups. The relative risk (RR) - odds ratio - was 1.9 and 1.4 respectively. Another study showed a prevalence of smokers of about 50% among hyperthyroid patients⁵⁵. Shine et al on the other hand⁵⁶, failed to confirm an increased prevalence of smokers among those with Graves' hyperthyroidism without relevant ophthalmopathy.

Until now, no definite mechanism has been provided for the influence of smoking on the prevalence of Graves' disease. In a recent review paper, Utiger²⁸ suggested that this might happen through different mechanisms, such as smoke-dependent structure alterations in TSH-receptor, making it more immunogenic, enhancement of responsiveness to factors responsible for the initiation of the disease or impairment of restoration of tolerance to thyroid autoantigens. Nevertheless, it has to be remembered that the nature of the disease may also influence smoking habits. It is well known that hyperthyroidism, when untreated, is associated with increased anxiety and nervousness and that uncontrolled psychosocial stress is associated with increased desire to smoke⁵⁷.

b. Graves' ophthalmopathy

Graves' ophthalmopathy, or thyroid eye disease (TED)^{58,59}, is the most frequent extrathyroidal clinical manifestation of Graves' disease and constitutes a major and complex pathogenetic and therapeutic dilemma²⁶. The first possible connection between cigarette smoking and Graves' ophthalmopathy was made by Hagg and Asplund⁶⁰ who showed that 10 out of 12 patients were current smokers, a figure much higher than that observed in Graves' patients without ophthalmopathy (46%) or in control subjects (31%). In addition, the prevalence of heavy smokers was higher in patients with more severe ophthalmopathy⁶⁰. Since then, there have been several confirmatory reports in both retrospective and prospective studies. In a cross-sectional study reviewing the smoking habits of patients with different thyroid diseases, Bartalena et al³⁶ found a 64% prevalence of smokers among patients with Graves' ophthalmopathy, a percentage much higher than that of Graves' disease without

eye involvement (48%), and 30% in patients with non-toxic goiter, toxic nodular goiter and Hashimoto's thyroiditis. These results were confirmed by other investigators^{13,24,36}. The same group²⁶ in a recent review paper estimated that the mean percentage of smokers among 732 patients with Graves' ophthalmopathy, compiled from 9 studies, was 67%. This percentage of smokers is much higher than that in patients without Graves' ophthalmopathy⁵³. Prummel et al²⁴, in a consecutive entry case control study, found that smoking greatly increased the risk of Graves' ophthalmopathy, with odds ratio of 7.7 (95% CI = 4.3-13.7). Furthermore, it seems that among patients with TED, smokers had more severe eye disease than non-smokers. No association has been found between the daily number of cigarettes consumed or the duration of smoking and the severity of TED²⁵. Pfeilschifter and Ziegler⁶¹, in a recent prospective study, showed that smoking patients with recent onset of Graves' thyrotoxicosis had a 1.3-fold increased incidence of clinically relevant Graves' ophthalmopathy, with 2.6 and 3.1-fold increases in the incidence of proptosis and diplopia respectively. In the same study, it was found that the current number, but not lifetime cigarette consumption, was an independent risk factor for the development of TED. Finally, Teller et al showed⁶² that the prevalence of ophthalmopathy correlated not only with smoking but also with ethnic origin. The percentage of smokers was higher in Caucasians than in Asian patients (42% and 7.7% respectively).

Smoking seems to influence not only the occurrence and the course of Graves' ophthalmopathy but also the response to various therapeutic interventions such as orbital radiotherapy and glucocorticoids administration⁶³. Bartalena et al⁶⁴ recently reported that in patients submitted to orbital radiotherapy and high-dose systemic glucocorticoid treatment for severe Graves' ophthalmopathy, a favorable response to treatment was observed in 61 of 65 non-smokers (94%) and only in 58 of 85 smokers (68%). Furthermore, among patients with mild Graves' ophthalmopathy, radioiodine treatment deteriorated eye disease in 0.5% of non-smokers and in 23% of smokers⁶⁴. A concomitant short-term course of oral glucocorticoid therapy could prevent this progression⁶⁵.

The etiology of endocrine ophthalmopathy is still unknown. The mechanism(s) of how cigarette smoking may affect the thyroid volume and especially the incidence and clinical severity of eye disease also remains unknown. Contents of cigarette smoke, hypoxia, formation of oxygen-free radicals⁶⁶ or direct irritative actions of smoking¹⁴ have all been implicated in triggering the

pathogenetic reaction of TED. Cigarette smoke is an irritant and can cause conjunctivitis and local irritation. This might not account, however, for the increase in volume of the extraocular muscles and/or of retrobulbar fibroadipose tissue. Smoking is also known to affect the immune system and autoimmunity is generally thought to play a role, although no specific ocular antigens have been identified as pathogens of TED. Hegedus et al⁶ found no differences in thyroid stimulating immunoglobulins (TSIS) among smoking and non-smoking healthy individuals. It is well accepted that cytokines play an important role in the pathogenesis of Graves' ophthalmopathy^{59,67,68}. Cigarette smoking may affect this process because smoking-induced hypoxia in the retrobulbar tissue has been shown to increase the release of cytokines from orbital fibroblasts and endothelial cells⁶⁹ and thereby may enhance the expression of adhesion molecules⁷⁰. It has been reported that compared to non-smokers, smokers had lower circulating levels of soluble interleukin receptor antagonist levels (sIL-1RA), an anti-cytokine antagonizing the effects of IL-1⁶⁶. However, a more recent study showed that sIL-1RA levels, both at baseline and during glucocorticoid treatment, are neither influenced by cigarette smoking nor predictive of subsequent response to glucocorticoid treatment⁷¹.

c. Chronic lymphocytic thyroiditis

In a longitudinal study of randomly selected samples of women, Nystrom et al¹⁰ demonstrated a strong association between smoking 12 years earlier and the subsequent development of autoimmune hypothyroidism, while smoking habits at the end of the investigation were not related to hypothyroidism. This association, however, has not been confirmed in other studies^{13,36}. As mentioned earlier, the prevalence of smokers was about 30% in patients with Hashimoto's thyroiditis, much lower than those with Graves' disease without (48%) or with ophthalmopathy (64%)³⁶.

Although both Graves' disease and Hashimoto's thyroiditis are two inter-related autoimmune disorders and they represent the two sides of the same coin, it is very interesting that they show such diversity in their relation to tobacco smoking. Therefore, other factors, possibly unrelated to a direct action of smoking on the immune system, might be implicated in the connection between Graves' disease and smoking

d. Pregnancy, fetal thyroid function and post-partum thyroid dysfunction

A highly significant correlation has been demonstrated between SCN- levels in the mother and cord blood, a

finding indicating that SCN- freely crosses the placenta⁷². An inverse correlation was found between SCN- levels in cord blood, birth weight, significantly decreased serum TSH levels and increased T4 levels in newborn babies of smoking mothers compared to non-smoking ones.

Thiocyanate has a biological half-life of 1-2 weeks²⁷. Therefore, measurements in plasma may be used to detect the degree of exposure to smoking from days to weeks after the last consumption. Gasparoni et al²⁷ found that infants whose mothers and fathers smoked had higher cord serum thyroglobulin and SCN- concentrations in comparison with infants whose parents did not smoke. The infants had no other evidence of thyroid abnormalities, such as increased T4,T3 or decreased TSH concentrations⁷³. Although thyroid size was not determined in this study, it has been reported to be increased in infants born from mothers who smoked⁷⁴. Of interest are two more findings from Gasparoni et al²⁷. First, that cord serum Tg levels were increased in the infants whose fathers, but not mothers, smoked, which means that the components of cigarette smoking that stimulate Tg secretion can be passively transferred to the infants, and secondly, that at age one of their lives, the same infants whose both parents smoked had higher serum Tg and SCN- concentrations than the infants whose parents did not smoke. Thus, smoking seems to induce similar changes in thyroid function in adults and the fetus. However, the fetus is, theoretical, more affected by these changes in thyroid function. Thus, these alterations may contribute to the growth retardation seen in babies born to smoking mothers⁷⁵.

The role of cigarette smoking in the development of post-partum thyroid dysfunction is not known. In a study of post-partum thyroid function in a group of 220 women, thyroid dysfunction was detected in 22% and was significantly related to smoking and to the presence of thyroid microsomal antibodies⁷⁶. However, this finding has not been confirmed^{72,77,78}.

CONCLUDING REMARKS

Based on recent available information, smoking exerts an influence on thyroid function through different mechanisms. Concerning thyroid hormone levels, smoking produces minor changes which are in general insignificant. The SCN- in smoke is most probably responsible for the goitrogenic action of smoking, especially in iodine deficiency areas.

There are some reports which have shown that smok-

ing has a protective effect on the incidence of thyroid cancer. However, many more studies are needed to confirm this effect and elucidate its mechanism.

The association between Graves' disease and smoking, and particularly Graves' ophthalmopathy and smoking, is much stronger and clearer. Smoking exacerbates thyroid eye disease and has a negative influence on the outcome of different therapeutic regimens and especially radioactive iodine. The mechanism is not yet fully understood. Regarding Hashimoto's thyroiditis and postpartum thyroiditis, no association with smoking has so far been disclosed.

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