Cigarette smoking and the thyroid

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The effects of smoking on the function of endocrine glands have been investigated extensively but still are to be elucidated fully. It is widely recognized that the most important component of the smoke produced from the burning of tobacco, in terms of endocrine effects, is nicotine. Nicotine acts through the interaction with acetylcholine receptors, but it seems likely that others among the numerous smoke products may somehow influence endocrine homeostasis. The present paper will focus on the relationship between smoking and variations in thyroid economy or the occurrence of thyroid dysfunction.

Thyroid function

Several studies have been carried out to ascertain whether smoking is associated with variations in thyroid economy. The rationale for these investigations was dictated by the observation that smoking is associated with a decrease in body mass, and, conversely, refrain from smoking is often accompanied by an increase in body mass (1). These changes might be mediated by variations in appetite and food intake but might also be linked to smoking-induced alterations in thyroid function. Melander et al. reported that cessation of smoking was associated with a small decrease in serum T4, reverse T3 (rT3) and a small increase in serum TSH levels, while serum T3 concentration was not altered significantly (2). These data were interpreted as being suggestive of the fact that cigarette smoking might stimulate thyroid function, which would be readjusted following smoking withdrawal. The fact that serum T3 levels were unchanged was interpreted as indicative of a selective stimulation of T4 secretion or, alternatively, of an increased T3 clearance caused by smoking.

Results obtained in subsequent studies are far from unequivocal, because T3 has been reported to be increased (3-5), unchanged (6-8) or slightly decreased (9, 10). Likewise, serum T4 has been found to be increased (6), normal (3-5, 7) or decreased (9, 10). Serum TSH concentrations in most cases were unchanged (3-5, 8) but also decreased values have been found (6, 7, 10). Interestingly, Sepkovic et al. observed that changes in T3, T4 and TSH concentrations were more pronounced in heavy smokers than in light-to-moderate smokers, while plasma thiocyanate levels progressively increased with the degree of smoking, implying a relationship between the increased absorption of cigarette smoke thiocyanate and the changes occurring in thyroid economy (9).

The conflicting results in the different series are not readily explainable. Several factors may have affected the results, including enrolment of heavy vs moderate smokers, the evaluation of short-term vs long-term effects and differences in age and body mass. In addition, differences might be related to the relative contribution of opposite mechanisms. If sympathetic nervous stimulation is prevailing, this might lead to stimulation of thyroid hormone secretion (11) and, in turn, to a decreased TSH release. On the other hand, the presence of substances in cigarette smoke that stimulate drug metabolism (12) might be responsible for a decrease in thyroid hormone levels, because induction of liver microsomal enzymes involved in the metabolism of thyroid hormones might result in an enhanced hormonal catabolism. The latter mechanism might also explain the observation that smoking is sometimes associated with an increase in serum T3 and a reduction in serum rT3 levels, a finding that might be related to an enhanced extrathyroidal formation of T3 at the expense of rT3. It is worth mentioning that the latter change is controversial because Edén et al. (6) found an increased rT3 concentration in smokers. Finally, to reconcile the finding of decreased thyroid hormone levels and normal/decreased TSH values reported by some authors (7), it should be postulated that an impairment of TSH secretion at the hypothalamic and/or pituitary level concomitantly occurs. No evidence for this effect of smoking has been provided so far and it must be mentioned that, at least under acute conditions (20 min of continuous smoking), cigarette smoking does not cause any significant variation in serum TSH levels (13).

Thus, cigarette smoking seems to be associated with minor and not unequivocal changes in thyroid function tests, but the pathophysiological relevance of these variations appears to be marginal.

Goiter

Several reports have documented that smoking is associated with an increased prevalence of goiter. Borup Christensen and co-workers (3) evaluated by palpation a population of 441 women and found that a palpable goiter was present in 25 of 169 smokers (14.8%) as compared to three of 80 ex-smokers (3.8%) and 18 of 192 non-smokers (9.4%). This was associated
with an increase in serum thyroglobulin (TG) concentration, while there was no relationship with the degree of smoking (3). Hegedus et al. (7) examined thyroid volume by ultrasound in 219 healthy subjects and observed that the prevalence of goiter was far higher in smokers (32 of 107, 29.9%) than in non-smokers (3 of 112, 2.7%), with a median thyroid volume of 26 ml in smokers and 15 ml in non-smokers (7). In agreement with the previous study, they also found an increase in serum TG concentration (7). In one study, although the size of goiter was not correlated with the number of cigarettes, heavy smokers appeared to have an increased frequency of nodular goiter (5). In a large epidemiological study carried out in Sweden and involving more than 4000 subjects, a higher prevalence of both non-toxic diffuse and nodular goiter was found in smoking women (14.2% vs 8.9% in non-smokers and 7% in ex-smokers) (8). It should, however, be pointed out that Bergvout et al. (14) failed to detect any significant difference in the thyroid volume in healthy smoking and non-smoking adults residing in a non iodine-deficient area. In the same subjects no correlation was detected between thyroid volume and daily tobacco consumption (14). It must be pointed out that the latter study was carried out on a cohort of subjects that was too small to draw any sound conclusion on this issue. The same group, in a subsequent case-control study carried out in the same region, reported that smokers were 45% among goitrous subjects and 40% among controls (15). A possible explanation for the discrepant results reported by the Dutch group is that their studies were carried out in iodine-sufficient areas. It is likely that cigarette smoking represents only a co-factor and its goitrogenic effect becomes more apparent when other goitrogenic factors, and particularly iodine deficiency, are also present. Recently, Petersen et al. (10) found that the prevalence of palpable goiters was 13.4% in non-smokers and 14.3% in smokers, and that of visible goiters did not differ in the two groups (2.1%). The observed discrepancy with most studies might be related to the fact that in the study by Petersen et al. (10) patients were older and it appeared likely that patients older than 50 years were less heavy smokers.

It is not completely clear how cigarette smoking can contribute to the development of goiter, but a candidate goitrogen in smoke is thiocyanate, produced by detoxification of hydrogen cyanide. The role of thiocyanate in the etiology of endemic goiter has been shown clearly in the presence of iodine deficiency (16). Body fluids of smokers contain increased thiocyanate concentrations (17). The increase in the thyroid volume/birthweight ratio in the newborn appears to parallel the increase in cord serum thiocyanate levels, taken as an index of maternal smoking habits, suggesting that smoking during pregnancy may be a relevant cause of thyroid gland enlargement in the newborn (18). The effects of thiocyanate and other cigarette smoking products (nicotine, cotinine) have also been studied in vitro using porcine thyroid follicles in culture (19): while nicotine and cotinine did not inhibit iodide transport or thyroid hormone synthesis, thiocyanate, at concentrations equivalent to those reached in the serum of smokers, inhibited iodide transport and iodine organification while increasing iodide efflux (19). In addition to underscoring the role of thiocyanate, these findings may explain the interaction of cigarette smoking and iodine deficiency in the development of goiter.

Thus, it would appear that smoking plays a significant role in the development of goiter, and most reports agree on a higher prevalence of goiter in smokers. Although it is conceivable that many (and yet unidentified) smoke products may contribute, thiocyanate appears to be the most likely culprit, in view of the high circulating levels found in smokers and of its complex effects on thyroid function. Smoking-related goitrogenesis appears to be frequent particularly in iodine-deficient areas, where smoke may represent also a relevant cause of neonatal thyroid enlargement.

Thyroid autoimmune disease

Cigarette smoking has a number of immunological effects involving both humoral and cellular components of the immune system (see Ref. 20 for a review). These include a depression of natural killer activity (21) and an increase in the total number of T lymphocytes (22), with a relative decrease in OKT4+ (helper) and an increase in OKT8+ (suppressor) subpopulations in heavy smokers (23). Serum immunoglobulin G (IgG), IgM and IgA levels are decreased by 10–20% in the serum of smokers (21), while IgE levels are increased in light-to-moderate smokers and decreased in heavy smokers (24). A lower level of immunosuppression has been observed in mice as an effect of smoking (25). The numerous immunological effects of smoking may have some relevance in human pathophysiology. For example, it has been shown that, while smoking is associated with Crohn’s disease, ulcerative colitis is strongly associated with non-smoking (26). The underlying mechanism might not necessarily be related to immunological effects of smoking, but to substances contained in smoke that might be somehow beneficial to ulcerative colitis patients. An association between rheumatoid arthritis and cigarette smoking has been reported (27), as well as an increased prevalence of anti-nuclear antibodies in smokers (28).

What is known about the relationship between smoking and thyroid autoimmune disease? A smoking-related immunological abnormality might be responsible for the higher prevalence of toxic diffuse goiters in smokers. Ericsson and Lindgarde observed that among 24 patients with Graves’ disease from a large epidemiological survey in Sweden, 17 were smokers (8). Likewise, we found that smokers were...
slightly less than 50% among 167 women with Graves’ disease (and no ophthalmopathy), a prevalence that is much higher than the 28% observed in normal controls (Table 1) (29). These results have been confirmed in a case-control study by Prummel et al. (15), who also reported a significant association between smoking and Graves’ disease (Table 1). It should be mentioned that, in disagreement with the above studies, Shine and co-workers failed to find any significant relationship between smoking and Graves’ hyperthyroidism (30).

What explanations can be offered for the increased number of cigarette smokers among Graves’ patients? Smoking might simply be an “innocent by-stander” and Graves’ patients might smoke more because they are stressed and nervous. The importance of negative stressful events in the pathogenesis of Graves’ disease has been reproposed recently by Winsa et al. (31), and stress is known to be associated with an increased desire to smoke (32). Alternatively, smoking might act by facilitating other activities (e.g. drinking alcohol, drinking coffee) or other factors that might be truly responsible for the occurrence of hyperthyroidism (33). However, it cannot at present be ruled out that smoking may represent one of the factors that directly come into play to precipitate Graves’ hyperthyroidism in genetically predisposed individuals. This concept would be supported by the observation that smoking is generally antecedent to the occurrence of hyperthyroidism. The effect of smoking could be accomplished by affecting immune surveillance and triggering autoimmune phenomena. In this regard it must be, however, underscored that the mentioned decrease in the ratio of helper to suppressor T lymphocytes in smokers is the opposite of what is commonly observed in patients with Graves’ disease (34).

In autoimmune thyroiditis, Fung et al. (35) reported that post-partum thyroid dysfunction, characterized either by transient hyperthyroidism or hypothyroidism, developed in 49 of 220 women (22%): in this series a significant correlation was found between the occurrence of post-partum thyroid dysfunction and smoking more than 20 cigarettes per day. This relationship (in particular with the development of long-term hypothyroidism after postpartum thyroid dysfunction) has not been confirmed in a subsequent study by the same group (36). Likewise, other studies have failed to correlate smoking with the occurrence of Hashimoto’s thyroiditis (8, 28, 29). It must be mentioned that a specific immunological role of anthracene derivatives in cigarette smoke cannot be ruled out completely, because 3-methylcholanthrene has been reported to cause experimental autoimmune thyroiditis in susceptible rats (37).

It is certainly surprising that two related autoimmune disorders such as Graves’ disease and Hashimoto’s thyroiditis show such a diversity in their relationship with cigarette smoking. This might somehow imply that the possible effect of smoking on the development of Graves’ disease would be unrelated to a direct action on the immune system. This remains to be demonstrated.

**Graves’ ophthalmopathy**

A possible relationship between cigarette smoking and Graves’ ophthalmopathy was first suggested in a small series of patients by Hagg and Asplund (38), who found that 10 out of 12 patients with Graves’ ophthalmopathy (83%) were current smokers, which is a proportion much higher than that observed in Graves’ patients without ophthalmopathy (11/24, 46%) or in controls (15/42, 36%) (Table 1). We confirmed this finding subsequently, in a large series of patients (29). In fact, we found that 64% of 307 Graves’ patients with ophthalmopathy were smokers and that the prevalence of heavy smokers was higher in patients with moderate-to-severe ophthalmopathy than in those with slight eye disease or, even more, in Graves’ patients without apparent ocular manifestations (Table 2) (29). These results were confirmed subsequently in a number of studies (Table 1). Shine and co-workers (30) reported that 53 out of 85 patients with Graves’ ophthalmopathy (62%) smoked, as compared to 27% of Graves’ patients.

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>N</th>
<th>Smokers</th>
<th>Graves hyperthyroidism*</th>
<th>N</th>
<th>Smokers</th>
<th>Graves' ophthalmopathy</th>
<th>Controls</th>
<th>N</th>
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<td>Hagg</td>
<td>1987</td>
<td>24</td>
<td>11 (46%)</td>
<td></td>
<td>12</td>
<td>10 (83%)</td>
<td></td>
<td>42</td>
<td>15 (36%)</td>
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<td>167</td>
<td>80 (48%)</td>
<td></td>
<td>307</td>
<td>197 (64%)</td>
<td></td>
<td>486</td>
<td>135 (28%)</td>
<td></td>
</tr>
<tr>
<td>Shine</td>
<td>1990</td>
<td>62</td>
<td>17 (27%)</td>
<td></td>
<td>85</td>
<td>53 (62%)</td>
<td></td>
<td>81</td>
<td>11 (14%)</td>
<td></td>
</tr>
<tr>
<td>Balazs</td>
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<td>45</td>
<td>10 (22%)</td>
<td></td>
<td>38</td>
<td>36 (95%)</td>
<td></td>
<td>12</td>
<td>11 (30%)</td>
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<tr>
<td>Tellez</td>
<td>1992</td>
<td>103</td>
<td>29 (28%)</td>
<td></td>
<td>52</td>
<td>23 (44%)</td>
<td></td>
<td>11</td>
<td>157 (39%)</td>
<td></td>
</tr>
<tr>
<td>Winsa</td>
<td>1993</td>
<td>208</td>
<td>85 (41%)</td>
<td></td>
<td>62</td>
<td>30 (48%)</td>
<td></td>
<td>372</td>
<td>112 (30%)</td>
<td></td>
</tr>
<tr>
<td>Prummel</td>
<td>1993</td>
<td>100</td>
<td>56 (56%)</td>
<td></td>
<td>100</td>
<td>81 (81%)</td>
<td></td>
<td>400</td>
<td>157 (39%)</td>
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<tr>
<td>Total</td>
<td></td>
<td>709</td>
<td>288 (41%)</td>
<td></td>
<td>656</td>
<td>430 (66%)</td>
<td></td>
<td>1381</td>
<td>430 (31%)</td>
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*Graves’ patients with apparently no ophthalmopathy.
without ophthalmopathy and 13–14% of controls. Balazs et al. (39) observed that 36 of 38 Hungarian patients with Graves’ ophthalmopathy were smokers, whereas only 10 of 45 patients without ocular manifestations smoked. In disagreement with others (40, 41), these authors also observed a strong association between eye disease and HLA-DR3 and/or B8 (39). Tellez et al. (42) reported that cigarette smoking produced a risk for developing ophthalmopathy that was 2.4 times higher than that observed in patients who never smoked. In the latter study a markedly lower prevalence of Graves’ ophthalmopathy was found in Asian patients, and this appeared attributable only in part to the lower frequency of cigarette smoking in Asian subjects (42). In a case-control study of 208 patients Winsa et al. found that among those with ophthalmopathy there were slightly more patients with a history of smoking and, more importantly, more current smokers when compared with the remaining group (43). These authors also confirmed a relationship between the degree and duration of smoking and the severity of ophthalmopathy (43). Prummel and Wiersinga (15), while confirming that cigarette smoking greatly increased the risk for the development of Graves’ ophthalmopathy and was in general associated with a more severe disease than in non-smokers, were unable to demonstrate a significant association between the number of cigarettes smoked per day or the duration of smoking and the severity of eye disease (Table 2). Finally, in a randomized study carried out on 171 patients assigned to different forms of treatment for hyperthyroidism, development or worsening of eye disease was more likely to take place in smokers than in non-smokers (44).

While the association between cigarette smoking and ophthalmopathy (and possibly also its severity) is widely recognized, the mechanisms whereby smoking affects eye disease remain to be clarified. One possibility is that smoking may have direct irritative effects. This, however, might explain the inflammatory changes involving soft tissues (tearing, burning, grittiness, conjunctival hyperemia) but not the increased volume of the extraocular muscles and/or the retrobulbar fibro-adipose tissue. Another possibility is that smoking may affect immune reactions involved in Graves’ ophthalmopathy. In addition to the previously mentioned smoking-related immunological abnormalities, smoking is goitrogenic and associated with an increase in serum TG concentrations (3, 7). This might lead to an increase in the titer of anti-TG antibodies and be relevant in the pathogenesis of Graves’ ophthalmopathy, because a structural homology exists between TG and acetylcholinesterase that is particularly abundant in the nerve/nerve and nerve/muscle junctions of the extraocular muscles (45). The significance of this homology and its pathophysiological significance in the development of Graves’ ophthalmopathy, however, have been questioned (46). Thyrotropin receptor transcripts have been identified recently in the eye-orbit structures (47, 48). Although other reports subsequently failed to demonstrate the presence of complete TSH receptor in orbital tissue (49), even the presence of non-functional TSH receptors in the orbital structures might be the antigenic link between the thyroid and the orbit, and autoantibodies to the TSH receptor might be stimulated by smoking and be involved in the development of thyroid-associated ocular disease. This hypothesis awaits a convincing demonstration.

The role of cytokines in the immune reactions occurring in the retroocular tissue has been proposed lately. Immunoreactivity for three cytokines (interferon-gamma, tumor necrosis factor alpha, interleukin 1 alpha) has been detected in retroocular connective tissue obtained during orbital decompression from patients with Graves’ ophthalmopathy (50); interleukin 1 and transforming growth factor-beta have been reported to stimulate glycosaminoglycan synthesis by retroocular tissue fibroblasts (51–53); several cytokines have been shown, using cultured retroocular fibroblasts from patients with Graves’ ophthalmopathy, to enhance the expression of heat shock proteins that are probably involved in the intracellular processing and cell surface presentation of antigens and, therefore, in triggering or maintaining the autoimmune reaction (54). Smoking might influence cytokine release and activity because, for example, interleukin 1 production is stimulated by tobacco glycoprotein (55). Recently, Metcalfe and Weetman (53) have demonstrated that retroocular fibroblasts exposed to hypoxia show an increased production of glycosaminoglycans, proteins and DNA, both basally and after cytokine stimulation. Thus smoking, by reducing oxygen tension, might cause

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**Table 2. Relationship between cigarette smoking and severity of Graves’ ophthalmopathy.**

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bartalena</td>
<td>1989</td>
<td>Increased prevalence of heavy smokers among patients with moderate to severe ophthalmopathy</td>
</tr>
<tr>
<td>Shine</td>
<td>1990</td>
<td>Increased prevalence of smokers among patients with severe ophthalmopathy</td>
</tr>
<tr>
<td>Tellez</td>
<td>1992</td>
<td>Increased prevalence of ophthalmopathy among heavy smokers</td>
</tr>
<tr>
<td>Winsa</td>
<td>1993</td>
<td>Increased prevalence of smokers among patients with severe ophthalmopathy</td>
</tr>
<tr>
<td>Prummel</td>
<td>1993</td>
<td>More severe ophthalmopathy in smokers: among smokers no relationship between degree of smoking and severity of ophthalmopathy</td>
</tr>
</tbody>
</table>
hypoxia and, thereby, exacerbate an ongoing orbital immune reaction triggered and/or maintained by cytokines. Smoking-induced hypoxia might contribute further to the pathogenesis of ophthalmopathy by causing cytokine-induced enhanced expression of adhesion molecules (56, 57).

Whether one or more of the above smoking-related mechanisms are effectively operating in vivo to contribute to the expression of Graves’ ophthalmopathy is a matter of controversy, but the association between smoking and eye disease appears to be well established.

Concluding remarks

The relationship between cigarette smoking and the thyroid is multifaceted and far from being completely understood. Marginal changes of thyroid function have been described in smokers, but an overall evaluation of reported series shows that these effects are controversial and, therefore, unlikely to have a relevant pathophysiological significance.

More clearly established is the goitrogenic effect of smoking, which is probably related to the action of thiocyanate (and possibly of other compounds liberated in smoke). This effect might be particularly important in iodine-deficient areas.

An interesting observation is the high prevalence of smokers among patients with Graves’ disease, but it is unclear whether this has a pathogenetic importance or merely represents an epiphenomenon of behavioural changes related to thyroid hyperfunction. Even more striking is the association between smoking and Graves’ ophthalmopathy. Although the underlying mechanisms need to be elucidated, smoking might have a role in the pathogenesis of Graves’ ophthalmopathy. In this regard, it would appear reasonable to suggest that patients with Graves’ ophthalmopathy refrain from smoking.

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