COMMENTARY

Smoking and autoimmune thyroid disease: the plot thickens

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Abstract

New studies have shown that smoking may protect against the development of thyroid peroxidase antibodies, which may result in a decreased risk of Hashimoto’s hypothyroidism (HH), whereas it stimulates the development of Graves’ hyperthyroidism (GH). According to the above-mentioned hypothesis, to stop smoking would decrease the risk of GH but increase the risk of HH. Also, smoking has been identified as one of the risk factors for the development or worsening of eye changes after 131I treatment of GH. Additionally, the outcome of medical treatment of Graves’ ophthalmopathy (GO) is less favourable in smokers as compared to non-smokers. There is concern also about the effect of passive smoking on autoimmune thyroid disease. In a recent study it has been shown that the latter may have a deleterious effect on childhood GO.

The association between smoking and autoimmune thyroid disease (AITD), as evident from epidemiological studies, has become common knowledge in the last decade. There is no doubt that smoking is a risk factor for the development of Graves’ hyperthyroidism (GH) and even more so for Graves’ ophthalmopathy (GO): all studies reach the same conclusion (1). The situation is less clear with respect to autoimmune hypothyroidism: some studies do report a higher prevalence of smokers presenting with Hashimoto’s hypothyroidism (HH) whereas others are unable to find such an association (1, 2). Studies on smoking and autoimmune hypothyroidism are, however, few in number and heterogeneous in nature, and a recent meta-analysis failed to detect a significant association, although there was a trend (1).

New studies provide fascinating insights into the relationship between smoking and AITD. Unexpectedly, they raise the possibility that smoking may prevent the occurrence of HH (whereas it stimulates the development of GH). The studies also allow an evidence-based approach to determining whether cessation of smoking diminishes the risk of Graves’ disease (GD) and whether passive smoking is relevant in this respect.

Smoking protects against thyroid peroxidase antibodies

There are now three studies that all imply that smoking may protect against the development of thyroid peroxidase antibodies (TPO-Ab). In 2003 Strieder and co-workers reported on risk factors for AITD in 759 euthyroid females with at least one relative with documented AITD (3). Current smoking (defined as smoking now, or having stopped smoking within 1 year of the study visit) was more prevalent in subjects without TPO-Ab (<100 kU/l) than in subjects with TPO-Ab ≥100 kU/l (38 vs 25%, P < 0.001). The frequency of ever smoking was similar between both groups (59 vs 52%, NS). Current smoking was an independent determinant for the presence of TPO-Ab with an odds ratio of 0.688 (95% CI 0.480–0.986). In 2004 Goh et al. likewise observed a lower prevalence of TPO-Ab in smokers than in non-smokers (52 vs 73%, P = 0.06) among 102 patients with newly diagnosed GH (4).

The largest dataset comes from the NHANES III study, conducted between 1988 and 1994 and reflecting the entire non-institutionalised US population. After excluding subjects taking thyroid-altering medications from the 18 148 persons who underwent thyroid testing, 15 592 remaining subjects were analysed (5). Subjects were classified as smokers if serum cotinine was >15 ng/ml. Fewer smokers (11%, 95% CI 10–19%) had thyroid antibodies (TPO-Ab ≥1.0 IU/ml) than non-smokers (18%, 95% CI 17–19%). The difference in prevalence of thyroid antibodies remained significant after adjustment for age, gender, race–ethnicity, and iodine status (Fig. 1). The relationship persisted upon analysing the association between smoking and the presence of TPO-Ab (independent of thyroglobulin-antibody (Tg-Ab) status), as was the case for Tg-Ab (independent of...
TPO-Ab status). The odds of having thyroid antibodies were lower by 1.1% for every 10 ng/ml increase in serum cotinine (OR 0.989, 95% CI 0.983–0.995). There was a significant inverse linear relationship between log (cotinine) and log (TPO-Ab) levels, even after adjusting for confounders. Smokers also less frequently had an elevated level of serum thyroid-stimulating hormone (TSH) of >4.5 mU/l than non-smokers (2.6%, 95% CI 2.0–3.2 vs 5.5%, 95% CI 4.7–6.3%; Fig. 1). The OR for TSH elevation in smokers was 0.5 (95% CI 0.4–0.6), and the odds were lower by 1.4% for every 10 ng/ml increase in serum cotinine. However, among persons without TSH elevation, smoke exposure was associated with 200% greater odds of having TSH levels of 0.1–0.4 mU/l (adjusted OR 2.0, 95% CI 1.3–2.9), and every 10 ng/ml increase in cotinine was associated with 2% higher odds.

It can be concluded that smoking in a dose-dependent manner is negatively associated with TPO-Ab and elevated TSH, and positively with subnormal TSH. A probable explanation of these findings is that smoking inhibits the development of TPO-Ab and thereby protects, to a certain extent, against the occurrence of chronic lymphocytic thyroiditis and consequently against an elevated TSH. This line of reasoning is supported by a slightly higher serum TSH in TPO-Ab positive than in TPO-Ab negative healthy subjects with TSH values all within the normal reference range (3), and by a Danish population study indicating a lower prevalence of subclinical hypothyroidism among self-reported smokers with an adjusted OR of 0.47 (95% CI 0.33–0.67) (6). In contrast, smoking appears to increase the risk of subnormal TSH values. Although the NHANES III study does not specify the cause of these subnormal TSH values, it might well be that these subjects are on their way to developing GH. Indeed, data from the large prospective Nurses Health Study II, with a 12-year follow-up, indicate cigarette smoking as a predictor of GH (7). The covariate-adjusted hazard ratio among current smokers was 1.93 (95% CI 1.54–2.43).

The hazard ratio increased with the intensity of smoking and was 2.63 (95% CI 1.71–4.04) among women smoking ≥25 cigarettes daily.

AITD is thought to develop in relation to a particular genetic background and to be triggered by environmental factors. Based on recently obtained epidemiological data it could be speculated that the smoking behaviour of those individuals genetically susceptible to AITD determines, to some extent, whether they will develop HH or GH. In view of the manifold but poorly understood effects of smoking on the immune system, such a hypothesis might not be too speculative. It could be tested experimentally whether or not smoke exposure directs thyroid autoimmunity away from cell-mediated towards humoral immune reactions.

**Does cessation of smoking prevent AITD?**

According to the above-mentioned hypothesis, to stop smoking would decrease the risk of GH but increase the risk of HH. It is unknown whether ex-smokers put themselves at higher risk of autoimmune hypothyroidism by quitting smoking. In the NHANES III study there were no significant associations between a history of prior, but not current, smoking and any thyroid outcome, although there were fewer smokers among the 454 individuals taking thyroid-related medication (16.6%, 95% CI 11.7–21.5) than among the individuals not reporting thyroid-altering medications (32.2%, 95% CI 30.5–33.8) (5). Whereas hypothyroidism is easily treatable, GH and especially GO can be more difficult to treat. It follows that, particularly in view of the many other adverse health outcomes associated with smoking, the standard advice should always be to discontinue smoking. The question that then arises is whether there is good evidence that the risk of GD becomes lower in ex-smokers. Vestergaard’s (1) meta-analysis indeed concludes that cessation of smoking lowers the risk of GH: the OR for current smoking
The effect of passive smoking

There is concern about the effect of passive smoking, in this respect best illustrated by the financial support from the Flight Attendant Medical Research Institute for the NHANES III study at the time when smoking was still permitted in aircraft. It is, however, very difficult to evaluate the effect of passive smoking. The only available circumstantial evidence that passive smoking might be a risk factor for AITD is derived from a questionnaire study on childhood GO (16). Out of 1914 patients with childhood GH seen by respondents from 23 countries in the last 10 years, 576 (30%) had GO. When grouped according to smoking prevalence among teenagers in the country of origin, it became evident that the proportion of GO patients among children with GH is highest in countries in which teenagers smoke most (Table 1). What is striking is that 52% of the children with GH in these countries (smoking prevalence ≥25%) are 10 years old or younger, whereas the figure (19%) is much lower in countries in which smoking prevalence among teenagers is less than 25%. It is unlikely that children ≤10 years of age smoke themselves; the high proportion of GO in this group is thus best explained by passive smoking as a result of

Table 1 Occurrence of childhood Graves’ ophthalmopathy in Graves’ hyperthyroidism as a function of smoking prevalence among teenagers in their country of origin.

<table>
<thead>
<tr>
<th>Smoking prevalence among teenagers*</th>
<th>Graves’ hyperthyroidism</th>
<th>Graves’ ophthalmopathy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≤10 years (%)</td>
<td>11–18 years (%)</td>
</tr>
<tr>
<td>(1) ≥25%</td>
<td>644 (100%)</td>
<td>236 (36.6%)</td>
</tr>
<tr>
<td>(2) 20–25%</td>
<td>818 (100%)</td>
<td>223 (27.3%)</td>
</tr>
<tr>
<td>(3) &lt;20%</td>
<td>452 (100%)</td>
<td>117 (25.9%)</td>
</tr>
</tbody>
</table>

living in an environment in which 25% or more of their peers smoke.

It is of interest that, based on the WHO regional office for Europe, tobacco control database, 2003, all the countries (100%) that are included in the first group have a smoking prevalence higher than 25% among adults, while only 50% and 40% of the countries in the second and third groups exhibit such a prevalence.

In conclusion, new studies have shown that smoking may protect against the development of TPO-Ab, which may result in a decreasing risk of HH, whereas it stimulates the development of GH. According to the above-mentioned hypothesis, to stop smoking would decrease the risk of GH but increase the risk of HH. Also, smoking has been identified as one of the risk factors for the development of eye changes after 

References


Received 17 January 2006
Accepted 3 March 2006