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.

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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 $\geq$ 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

Figure 1 Prevalence of thyroid autoantibodies and elevated TSH concentrations among non-active smokers and active smokers, excluding subjects taking thyroid-related medications. Adjustments include age, gender, race–ethnicity, and urinary iodine. Individuals with TSH levels below 0.1 mU/l were excluded from the analysis of TSH elevation. Lines represent 95% CIs. From RM Belin *et al.* (5), with the permission of the Endocrine Society.

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 cofounders. 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

(3.30, 95% CI 2.09–5.22) is higher than for previous smokers (1.41, 95% CI 0.77–2.58, $P=0.047$). Even better evidence can be derived from the Nurses Health Study II, in which the covariate-adjusted hazard ratio among past smokers was 1.27 (95% CI 1.03–1.56) vs 1.93 (95% CI 1.54–2.43) among current smokers (7). The hazard ratios decreased with the number of years since a past smoker had stopped smoking, from 0.83 at 5 years to 0.52 at >15 years since quitting ($P=0.002$ for trend; hazard ratio for current smokers set at 1.00). It should be added that four observational studies have now been published, all indicating a higher recurrence rate of GH in smokers than in non-smokers following a course of antithyroid drugs. A Belgian study reported a relapse risk in patients without TSH receptor antibodies at the end of the drug course of 18% in non-smokers and of 57% in smokers; in the case of positive TSH receptor antibodies these figures were 86% in non-smokers and 100% in smokers (8). Similar figures have been reported in a Norwegian study: after withdrawal of antithyroid drugs the relapse rate in smokers was higher than in non-smokers (58 vs 39%, $P=0.009$) (9). A British study reported that smoking had a marginally significant ($P=0.081$) deleterious effect on the likelihood of remission after antithyroid drug treatment for GD. The effect of smoking was, however, highly significant in males and indeed the deleterious effect on remissions may be restricted to males (OR 11.1, 95% CI 1.25–98.5) (10). Finally, a German study has also indicated smoking as an independent risk factor for recurrent GH (11). Taken together, the available studies provide good evidence that cessation of smoking is beneficial in both primary and secondary prevention of GH.

Smoking is a risk factor for GH but the odds for GO are much higher (1.9, 95% CI 1.1–2.7 vs 7.7, 95% CI 4.3–13.7 in a case-control study on GH without and with eye changes respectively) (12); the odds increase progressively with more severe eye disease. Smoking has been identified as one of the risk factors for the development or worsening of eye changes after ^{131}I treatment of GH (13). The outcome of immunosuppressive treatment (glucocorticoids, retrobulbar irradiation) of GO is less favourable in smokers as compared to non-smokers (13, 14). The data certainly suggest that refraining from smoking is useful in the secondary and tertiary prevention of GO; definite proof is lacking in this

respect, however, because formal trials on smoking cessation in GO patients have not been undertaken. The best evidence for primary prevention of GO by quitting smoking comes from a study by Pfeilschifter and Ziegler (15). They report, among current smokers, a relative risk (RR) of diplopia of 1.8 (95% CI 0.8–4.3) at 1–10 cigarettes per day; the RR is 3.8 (95% CI 1.9–9.7) for 11–20 cigarettes per day, and 7.0 (95% CI 3.0–16.5) for >20 cigarettes per day, with similar figures for pre-optosis. Among ex-smokers who smoked >20 cigarettes per day, the RR for diplopia is 1.9 (95% CI 0.5–7.7), and is no longer significant. As patients with GO are very much concerned (and rightly so) about their visual functions and appearance, the physician should grasp the opportunity to convince their patients to stop smoking. It is very likely to improve the outcome of the eye disease, and, because of their eye changes, patients might be more inclined than at other times to follow the advice to stop 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 1 914 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 GO in these countries (smoking prevalence $\geq 25\%$) 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.

Smoking prevalence among teenagers*	Graves' hyperthyroidism	Graves' ophthalmopathy	Graves' ophthalmopathy	
			≤ 10 years (%)	11–18 years (%)
(1) $\geq 25\%$	644 (100%)	236 (36.6%)	52	48
(2) 20–25%	818 (100%)	223 (27.3%)	15	85
(3) <20%	452 (100%)	117 (25.9%)	24	76

*Data per country based on WHO regional office for Europe, tobacco control database, 2003. Internet: <http://data.euro.WHO.int/tobacco>.

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 or worsening of eye changes after ^{131}I treatment of GH. Additionally, the outcome of medical treatment of GO is less favourable in smokers than non-smokers. There is concern also about the effect of passive smoking on AITD. In a recent study it has been shown that the latter may have a deleterious effect on childhood GO.

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