J. Endocrinol. Invest. *25:* 152-157, 2002

Does smoking increase relapse rates in Graves' disease?[1]

L.E. Kimball*, E. Kulinskaya**, B. Brown*, C. Johnston*, and N.R. Farid*,**

*The Department of Endocrinology, Hemel Hempstead General Hospital, Hemel Hempstead;
**University of Hertfordshire, Hatfield, Hertfordshire, United Kingdom

ABSTRACT. We wondered whether the relapse rate of Graves' hyperthyroidism was increased amongst patients who smoked. To this end, a retrospective analysis of clinical and laboratory data of consecutive patients with Graves' disease was carried out. All patients were treated with thionamide anti-thyroid drugs (ATD) for at least one year and remission was defined as continued and biochemical euthyroidism, at least 6 months after discontinuing ATD. The study comprised 221 subjects with Graves' disease from a hospital-based population over 9 years. We took the following variables into account when assessing contribution to disease relapse: Goiter, Thyroid Associated Ophthalmopathy (TAO), and Time to euthyroidism after starting ATD and interaction between smoking and sex. Smoking had a marginally significant (*p*=0.081) deleterious effect on the likelihood of remission after ATD treatment for Graves' disease. The effect of smoking was, however, highly significant in males and indeed the deleterious effect on remissions may be restricted to males (odds ratio, 11.1; 95% confidence interval, 1.25 to 98.5). The presence of goiter (odds ratio, 3.8; 95% confidence interval, 2.05 to 7.1) and TAO (odds ratio, 1.8; 95% confidence interval, 0.993 to 3.18) forecasted lower chances of achieving remission. The shorter the time a patient became euthyroid after starting ATD the more likely his disease was to remit. We conclude that cigarette smoking increases the likelihood of Graves' disease recurrence in males treated with anti-thyroid drugs. Thus, smoking appears to be an important risk factor in the pathogenesis and outcome of Graves' disease patients at least in subsets of patients.

(J. Endocrinol. Invest. *25:* 152-157, 2002)

©2002, Editrice Kurtis

INTRODUCTION

Cigarette smoking is an important risk factor in the pathogenesis and outcome of an increasing number of diseases. Smoking is the most visible environmental risk factor for Thyroid Associated Ophthalmopathy (TAO). It has been suggested that smoking may influence ophtalmopathy through direct irritative effects or by modulating immune reactions that occur in Graves' disease. Smoking probably also adversely influences the outcome of the therapy of eye disease. Specifically, smoking and the degree of smoking have been found to affect the outcome of orbital radiation therapy and high-dose glucocorticoid treatment in patients with severe ophthalmopathy (1).

We have previously identified two subsets of Graves' disease patients, which differed in severity and prevalence of TAO. Patients with severe disease had high rates of disease recurrence after withdrawal of anti-thyroid drugs, large goiters, family history of the disease, laboratory parameters of autoaggression and high prevalence of Major Histocompatibility Complex susceptibility alleles for Graves' disease (2, 3). The influence of smoking on disease relapse rate has not been previously specifically addressed.

Graves' disease is characterized by remissions and relapses and many factors affect the length of remission following the cessation of anti-thyroid therapy (4-10). We wondered whether smoking has an influence on remission rate in patients treated with anti-thyroid drugs. To this end, we retrospectively analyzed the clinical and laboratory data from a large group of patients with Graves' disease treated with anti-thyroid drugs. From this we sought to answer the question of whether smoking is associated with higher recurrence rates of Graves' disease.

---

[1]Presented in part at the Annual Meeting of the Endocrine Society, San Diego, Ca, June 12-15, 1999.

Key-words: Graves' disease, remission, antithyroid drugs, smoking, logistic regression.

Correspondence: Prof. Nadir R. Farid, Osancor Biotech Inc, 31 Woodland Drive, Watford, Herts WD17 3BY, UK.

E-mail: farid@osancor96.fsnet.co.uk

Accepted August 27, 2001.

SUBJECTS AND METHODS

This study identified 263 patients with Graves' disease visited at West Hertfordshire, England over 9 yr (1988-1996). Two hundred and twenty-one were deemed to have complete evaluable records and met the diagnostic, therapeutic and follow-up criteria of the study. All patients were treated with antithyroid drugs (ATD) for at least one year (range 12 to 96 months). Remission was defined as continued clinical and biochemical euthyroidism at least 6 months after discontinuing ATD. This cut-off point is not without precedent, was logistically convenient and valid in that, in retrospect, >90% of a smaller subset of patients who were in remission at 6 months were so at the end of a one year of follow-up.

Characteristics examined included sex, age, age at diagnosis of Graves' disease, smoking, goiter size, presence of TAO (11), serum thyroid hormone levels, thyroid auto-antibody levels, time to chemical euthyroidism after institution of ATD and total duration of therapy. These characteristics were related to remission of Graves' hyperthyroidism. Smoking status was determined at the time of diagnosis and because of the nature of this retrospective data analysis the quantity of cigarettes smoked was difficult to ascertain. Patients were regarded as smokers, ex-smokers or non-smokers at the time of diagnosis. In this study the attribute "smoking" applies to current smokers.

Inspection and palpation at the time of diagnosis estimated thyroid size on a scale of: 0-4 (0=normal thyroid; 1=small, 2=medium, 3=large and 4=very large goiter) based on an estimated thyroid weight of 20 g (grade 0) for a normal thyroid and ≥40 g for a very large thyroid (grade 4). Serum samples were drawn at the time of diagnosis for analysis of T_3, T_4, free T_4 and TSH. Total T_3, T_4, fT_4 and TSH were measured using double-antibody radioimmunoassays, the normal reference ranges being 1.2-3.0 nmol/l for T_3, 70-140 nmol/l for T_4, and 9-22 pmol/l for free T_4. A basal TSH level <0.5 mU/l was regarded as pathological. TG and thyroid microsomal antibodies were measured with a solid-phase immunosorbent radioassay. TSH receptor antibodies were not measured.

The total study group consisted of 221 patients. The average age of the overall group was 41.73 yr±13.7 (±SD). One hundred and twenty-nine (58.4%) patients were considered to have some degree of TAO. Seventy (31.7%) were current smokers and 25 (11.3%) had recently stopped smoking.

One hundred and eighty-three patients (82.8%) were female. Of these hyperthyroidism remitted in 53 (29%). Of the subgroup with remitting Graves' disease, 15 (28%) were smokers, 28 (53%) had TAO, 16 (30%) were goitrous (goiter 2-4), and 39 (74%) had serum thyroglobulin Ab titers >1/40. In the subgroup with relapsing disease (no.=130), 42 (32%) were smokers, 81 (62%) had TAO, 80 (62%) were goitrous, and 115 (89%) had thyroglobulin Ab titers >1/40.

Of the 38 (17.2%) male patients, Graves' disease remitted in 13 (34%). Only 1 patient (8%) of the subgroup with remitting disease was a smoker: 4 (31%) had TAO, 3 (23%) were goitrous, and 7 (54%) had thyroglobulin Ab titers >1/40. Of the 25 with relapsing disease, 12 (48%) were smokers, 16 (64%) had TAO, 14 (56%) were goitrous, and 20 (80%) had thyroglobulin Ab titers >1/40.

Statistical analysis

The SPSS package was used for our statistical analysis. Analyses of the effect of categorical attributes on the odds against remission were performed using Fisher's exact test. Odds ratios with 95% confidence intervals were also calculated. The Mann-Whitney test was used to analyze differences in continuous characteristics between the patients whose disease remitted and those with recurrent disease. Normal approximation was used to calculate the standardized normal value (Z), and the *p*-value. Logistic regression analysis was used to explore different models of attributes to predict remissions.

RESULTS

Sixty-six patients (53 women and 13 men) achieved remission of Graves' disease. This is 29.9% of total number of patients. The average age of those whose disease remitted was identical to those with recurrent disease (41.76 yr±13.7 *vs* 41.86 years ±13.11).

The influences of categorical attributes, *e.g.* sex and smoking on likelihood of remission, were examined and are shown in Table 1. Fisher's exact test was used to test for associations. Odds ratios and 95% confidence intervals were also calculated. Seventy (31.7%) patients were current smokers, and 25 (11.3%) were ex-smokers. Among all of the patients, hyperthyroidism was in remission in 29.9%. In descending order of odds ratios cigarette smoking in males, the presence of goiter, anti-thyroglobulin antibody titer (as a measure of thyroid-specific autoimmunity) of 40 or greater and TAO vitiate against a person with Graves' disease treated with ATD for at least one-year achieving remission. It is noteworthy that only 1 of 13 males who smoked achieved remission.

We next examined continuous characteristics, as well as potential interactions between categorical

Table 1 - *Effect of categorical attributes on the odds against remission.*

Attribute	Odds ratio* (95% CI)	Significance (Fisher's exact test, one sided)
Sex (female)	1.275 (0.607-2.680)	0.322
Smoking	1.671 (0.870-3.209)	0.081
Female	1.209 (0.599-2.439)	0.365
Male	11.077 (1.245-98.548)	0.013
TAO	1.778 (0.993-3.180)	0.037
Goiter	3.817 (2.045-7.092)	0.000015
Thyro-Ab titer**	2.935 (1.451-5.936)	0.003

TAO=thyroid associated ophthalmopathy; thyro-Ab titer=thyroglobulin antibody titer. *Odds ratio against remission. **In this analysis 1/40 titer was used as a division between positivity or otherwise for thyroglobulin antibodies.

and continuous attributes, which may influence remissions of Graves' hyperthyroidism. Mann-Whitney (U) was used to analyze this aspect of the data. Normal approximation was used to calculate the standardized normal value (Z), and the *p*-value.

The data in Table 2 shows that the speed with which euthyroidism is achieved with ATD drugs predicts remissions. This is also reflected in the mean length of therapy. Interestingly, in this data set younger women rather than older men were more likely to go on to remissions. Median age of females whose Graves' disease went into remission was 41 yr than compared to 46 in those who did not remit; whereas for men the median ages were respectively 57 and 46 yr. Likewise, for those in remission, women were significantly younger at diagnosis than men (U=171.5, p=0.0026).

To further explore the effect of smoking on likelihood of remission controlling for other categorical attributes influencing remission, we examined eight different subgroups of patients varying in presence/absence of ophtalmopathy, thyroglobulin antibodies titer of 40 or greater, and goiter. Results are shown in Table 3 for female and male patients separately. Fisher's exact test was used to test for the association of smoking with remission of Graves' disease. There were no significant effects of smoking. The reason for this negative finding may well be the small subgroup sizes. This simple analysis is included to explain the necessity for more sophisticated multivariate analysis to follow, *i.e.* the logistic regression analysis.

We next sought to explore multivariate models in which we factored in the above attributes and that would allow us to predict remissions. For this we used logistic regression analysis. We investigated the following possible predictors for remission: goiter size (0-3), presence of TAO, presence of thyroid auto-antibodies, time to euthyroidism after starting ATD, main effects and interaction between smoking and gender, age and its interaction with gender. Of the large number of models explored we favor the one given in Table 4, which takes into account goiter size (p=0.0007), presence of thyroid auto antibodies (p=0.0021), gender (p=0.0276), time to euthyroidism (p=0.000), and an interaction of age

Table 2 - *Continuous variables influencing remission for all patients and for males and females separately. Values are median (interquartile range).*

	Remission (no.=66)	No remission (no.=155)	U	Z	*p*-value (one-sided)
Time to Eu* (months)	5 (3-7)	7 (4-10)	3698.5	-3.2694	0.0006
Time of Rx (months)	14 (13-17)	18 (15-25)	3276.5	-4.240	0.00001
Age of women (years)	41 (34-50)	46 (37-57)	2888.0	-1.714	0.043
Age of men (years)	57 (49-64)	46 (40-54)	107.0	-1.709	0.044
Diagnosis age, women (yr)	37 (30-47)	39.5 (30-50)	3151.0	-0.905	0.183
Diagnosis age, men (yr)	54 (44-62)	42 (33-48)	94.0	-2.111	0.0175

*Eu=euthyroidism. Time to euthyroidism refers to the period between onset of therapy with anti-thyroid medications and the normalization of thyroid function.

Table 3 - *Effect of smoking on remission, controlling for other categorical attributes influencing remission for men and women separately. Values are numbers (percentages) in each subgroup.*

Sex	Smoking	TAO	Thyroglobulin Ab titer*	Goiter**	Relapse	Remission	Total	*p*-value, Fisher's exact test
Female	No	No	No	No	1 (50%)	1 (50%)	2	1.0
	Yes				1 (33%)	2 (67%)	3	-
	No	Yes	No	No	4 (67%)	2 (33%)	6	0.524
	Yes				1 (25%)	3 (75%)	4	-
	No	No	Yes	No	13 (56%)	10 (44%)	23	1.0
	Yes				3 (60%)	2 (40%)	5	-
	No	No	No	Yes	3 (43%)	4 (57%)	7	1.0
	Yes				1 (100.0%)	-	1	-
	No	Yes	Yes	No	18 (60%)	12 (40%)	30	1.0
	Yes				9 (64%)	5 (36%)	14	-
	No	Yes	No	Yes	3 (75%)	1 (25%)	4	1.0
	Yes				1 (50%)	1 (50%)	2	-
	No	No	Yes	Yes	16 (80%)	4 (20%)	20	1.0
	Yes				11 (85%)	2 (15%)	13	-
	No	Yes	Yes	Yes	30 (88%)	4 (12%)	34	0.298
	Yes				15 (100.0%)	-	15	-
	Total				130 (71%)	53 (29%)	183	-
Male	No	No	No	No	1 (33%)	2 (67%)	3	1.0
	Yes				1 (100%)	-	1	-
	No	Yes	No	No	-	2 (100%)	2	0.333
	Yes				1 (100%)	-	1	-
	No	No	Yes	No	2 (33%)	4 (67%)	6	0.429
	Yes				1 (100%)	-	1	
	No	No	No	Yes	-	2 (100%)	2	N/A
	Yes				-	-	-	
	No	Yes	Yes	No	3 (60%)	2 (40%)	5	1.0
	Yes				2 (100%)	-	2	-
	No	Yes	No	Yes	2 (100%)	-	2	N/A
	Yes				-	-	-	-
	No	No	Yes	Yes	3 (100%)	-	3	0.400
	Yes				1 (50%)	1 (50%)	2	-
	No	Yes	Yes	Yes	2 (100%)	-	2	-
	Yes				6 (100%)	-	6	-
	Total				25 (66%)	13 (34%)	38	

*In this analysis thyroglobulin Ab titers >1/40 were considered positive. **Goiter scores 2-4 taken as positive. TAO: thyroid associated ophthalmopathy; Ab titer: antibody titer.

with gender (p=0.0184). From Table 4 we can see that goiter size of 2 or above carries a significant risk of non-remission. The comparatively short time to euthyroidism after starting ATD, age (being younger for females, and older for males), and absence of thyroid antibodies are all predictive of remission. The quality of this model is explored in Table 5. In this model prediction of remission for patients with remitting disease (sensitivity) is correct in 45.5% of cases and prediction of relapse for patients whose hyperthyroidism relapsed (specificity) is correct in 89.7% of cases. Overall correct prediction (remission/no remission) is 76.5%. The predictive value of this model is quite high. Prediction of relapse (negative predictive value) is correct in 81.41% and prediction of remission (positive predictive value) is 64.8% (Table 5).

Inclusion of TAO (p=0.1507) improved sensitivity of the above model to 50%, at the expense of a reduction of specificity to 87.7%. Further inclusion of

Table 4 - *Logistic regression to predict remission. Regression coefficients, adjusted odds ratios (OR) for remission and 95% confidence intervals for ORs. Goiter categories 0-3 are compared to the highest goiter category (4); OR of females to males; OR of thyroid antibodies being negative; OR of each extra month to euthyroidism*; OR of extra year of age for females**.*

Predictor	Regression coefficient (B)	*p*-value, Wald test	Adjusted odds ratio [Exp(B)]	95% Confidence interval for adjusted odds ratio	
				Lower	Upper
Gender (F)	2.8626	0.0276	17.5067	1.371	223.541
Goiter	-	0.0007	-	-	-
Goiter 0	2.5046	0.0045	12.2383	2.1743	68.8853
Goiter 1	2.8622	0.0008	17.5001	3.2912	93.0536
Goiter 2	1.5115	0.0992	4.5335	0.7519	27.3362
Goiter 3	1.7266	0.0564	5.6217	0.9541	33.1249
Thyro-Ab titer	1.2562	0.0021	3.512	1.579	7.8113
Time to Eu	-0.1425	0.000	0.8672	0.8117	0.9263
Age*sex (F)	-0.0598	0.0184	0.9419	0.8962	0.9900

*Adjusted odds ratio below 1 means the longer the time a patient became euthyroid after starting thionamide anti-thyroid drugs (ATD) the less likely his disease was to remit. **Adjusted odds ratio below 1 means the older a female patient was the less likely her disease was to remit. EU: euthyroidism; Ab titer: antibody titer.

Table 5 - *Logistic regression to predict remission. Quality of prediction for the model given in Table 4.*

Remission	Predicted		Total	Percent correct
Observed	No	Yes		
No	139	16	155	89.68%
Yes	36	30	66	45.45%
Total	175	46	221	
Predictive value	81.47%	64.8%		
Overall correct prediction	139	30	221	76.47%

smoking (p=0.4476) and its interaction with gender (p=0.2029) somewhat increased sensitivity to 53% without changing specificity of 87.7%. To summarize, neither TAO, nor smoking and its interaction with gender were significant factors, the latter being perhaps the result of comparatively small number of males (38) in this study.

DISCUSSION

The remission rate of 30% achieved in this study is the lower end of the spectrum quoted in the literature but is in line with many recent studies (4-10). The principal question we sought to answer was whether smoking was associated with higher recurrence rates of Graves' disease. The deleterious effect of smoking on remission rates was of marginal significance in the study group as a whole. In male patients the relationship of smoking to recurrent disease was highly significant (p=0.013) and indeed the effect of smoking was restricted to males. This finding raises the possibility that males are intrinsically susceptible to the immunologic and other effects of smoking, resulting in severe disease characterized by high recurrence rates after ATD treatment and high prevalence of TAO.

This study upholds the reasonable expectation that mild Graves' disease is likely to respond more rapidly to standard doses of thionamides as compared to more severe disease (2, 3, 9, 10). It follows that, on average, patients with milder disease receive treatment for a shorter period than those with severe disease. The latter statistic also reflects the reluctance (in the past) of physicians to refer patients with apparent non-remitting disease for radio-iodine therapy.

Some of the determinants of remission such as goiter size, surrogate markers of auto-aggression and rapidity with which euthyroid status is achieved after ATD affirm previous observations (2, 3, 9, 10). Although not measured in this study, TSH receptor antibodies have been noted to be less valuable in predicting remission than more simple clinical and immunologic measures (2, 6, 10).

TAO contribution in forecasting disease severity is worthy of special consideration. Thus, while it was significant in the examination of categorical attributes (Table 1), it did not contribute significantly to the logistic regression model because its effect was confounded with that of some of the other variables already in regression. As such it did not add any further information to the model.

The lack of predictive power of some of the factors *e.g.* familiarity (2, 3) may have to do with the fact

that the study was retrospective, extended over several years involving several observers scoring manifestations without explicitly agreed upon criteria. This probably also applies to the stratification of eye disease but not its presence.

At the other end of the scale some of the influences such as greater likelihood of remission with decreasing age in females and increasing age in males contradict earlier findings (2, 3, 10). The contribution of this aspect of the study to our remission model was of marginal significance.

The question we asked in initiating this study was whether or not smoking influences the remission rate of Graves' hyperthyroidism. Broadly, the answer is in doubt. There was, however, marked heterogeneity of risk between males and females in this respect – with smoking having a major negative impact on remission in males but not in females. This finding, along with the reported higher prevalence of TAO in males in many studies (1), and perhaps other difference in genetic susceptibly (12), suggest an important interaction between smoking and maleness in determining disease severity. Apparently life stresses (13, 14) and smoking independently (13) impact on the risk of developing Graves' hyperthyroidism in females but not males (13). It is thus possible that smoking may have an influence instead, on disease severity in males. Interestingly, the risk of smoking for Graves' disease in females may show marked age stratification (15).

The findings of the current study and the caveats raised by it suggest that a prospective study of smoking habits in patients with Graves' disease and its impact on disease severity might be worthwhile.

REFERENCES

1. Bartalena L., Pinchera A., Marcocci C. Management of Graves' ophthalmopathy: Reality and perspectives. Endocr. Rev. 2000 *21:* 168-199.
2. Stenszky V., Balazs C., Kozma L., *et al.* Identification of subsets of patients with Graves' disease by cluster analysis. Clin. Endocrinol. 1983, *18:* 335-345.
3. Frecker M., Preus M., Kozma L., *et al.* Heterogeneity by cluster analysis techniques of Graves' patients typed for HLA DR and IgG heavy chain markers. Mol. Biol. Med. 1986, *3:* 63-71.
4. McKenzie J.M. Does LATS cause hyperthyroidism in Graves' disease? (A review biased towards the affirmative). Metabolism 1972, *21:* 883-894.
5. Wartofsky L. Low remission after therapy for Graves' disease. Possible relation of dietary iodine with antithyroid therapy results. JAMA 1973, *226:* 1083-1088.
6. Schleusener H., Schwander J., Fischer C., *et al.* Prospective multicentre study on the prediction of relapse after antithyroid drug treatment in patients with Graves' disease. Acta Endocrinol. (Copenh.) 1989, *120:* 689-701.
7. Solomon B.L., Evaul J.E., Burman K.D., Wartofsky L. Remission rates with antithyroid drug therapy: continuing influence of iodine intake? Ann. Intern. Med. 1987, *107:* 510-512.
8. Allannic H., Lorcy Y., Leguerrier A.M., *et al.* Synthetic antithyroid drugs and Basedow's disease or the choice of a therapeutic strategy. Presse Med. 1991, *20:* 645-646.
9. Cooper D.S. Antithyroid drugs for the treatment of hyperthyroidism caused by Graves' disease. Endocrinol. Metab. Clin. North Am. 1998, *27:* 225-247.
10. Vitti P., Rago T., Chiovato L., *et al.* Clinical features of patients with Graves' disease undergoing remission after antithyroid drug treatment. Thyroid 1997, *7:* 369-375.
11. Classification of eye changes of Graves' disease. Thyroid 1992, *2:* 235-236.
12. Tellez M., Cooper J., Edmonds C. Graves' ophthalmopathy in relation to cigarette smoking and ethnic origin. Clin. Endocrinol. (Oxf.) 1992, *36:* 291-294.
13. Yoshiuchi K., Kumano H., Nomura S., *et al.* Stressful life events and smoking were associated with Graves' disease in women, but not in men. Psychosom. Med. 1998, *60:* 182-185.
14. Winsa B., Adami H.O., Bergstrom R., *et al.* Stressful life events and Graves' disease. Lancet 1991, *338:* 1475-1479.
15. Ericsson U.B., Lindgarde F. Effects of cigarette smoking on thyroid function and the prevalence of goiter, thyrotoxicosis and autoimmune thyroiditis. J. Intern. Med. 1991, *229:* 67-71.