Impact of smoking on the response to treatment of thyroid associated ophthalmopathy

A Eckstein, B Quadbeck, G Mueller, A W Rettenmeier, R Hoermann, K Mann, P Steuhl, J Esser

Background: In patients with Graves’ disease, smoking considerably increases the incidence and severity of thyroid associated ophthalmopathy (TAO). The authors sought to determine if smoking also influences the course of TAO during treatment, and the efficacy of therapy.

Methods: 41 smokers and 19 non-smokers with moderate untreated TAO were included in this prospective study. All patients were treated with steroids and, 6 weeks after the beginning of drug therapy, with orbital irradiation. Follow up was performed 1.5, 4.5, 7.5, and 12 months after the beginning of the study. Proptosis, clinical activity score (CAS), and motility were evaluated. The extent of smoking was derived from the concentration of the haemoglobin adduct N-2-hydroxyethylvaline (HEV), a parameter of long term smoking.

Results: There was no difference in the clinical manifestations of TAO between smokers and non-smokers at the beginning of treatment. However, CAS decreased (p<0.05) and motility improved (p<0.02) significantly faster and to a greater extent in non-smokers than smokers. Inverse correlations between the CAS decrease and the HEV levels observed 4.5 and 7.5 months after the beginning of treatment and between the improvement of motility and the HEV levels after 1.5, 4.5, and 7.5 months indicated a dose dependence. Mean HEV levels did not vary much during the follow up period and were significantly different in smokers (mean 5.4 (SD 2.7) µg/l) and non-smokers (mean 1.8 (1.3) µg/l; p<0.01).

Conclusion: Smoking influences the course of TAO during treatment in a dose dependent manner. The response to treatment is delayed and considerably poorer in smokers.

Patients and methods

Patients

The prospective study included 67 patients with active TAO of moderate severity (manifestation less than 12 months before the beginning of the study). Sixty patients completed a 1 year follow up period. The data of these patients were statistically evaluated. Five patients were lost during the follow up period owing to a lack of compliance or a change of residence. Two were excluded because of radioiodine therapy. Among the patients who completed the study, 41 were smokers (11 men and 30 women, mean age 46 (18–70) years) and 19 non-smokers (four men and 15 women, mean age 47 (30–69) years).

Thyroid status of the patients was mainly euthyroid with overt hyperthyroidism or hypothyroidism (because of overtreatment). Thyroidal function was not significantly different in smokers and non-smokers at the time of the initial presentation (Table 1) and during the course of the study (data not shown). TSH receptor antibodies were elevated in the majority of patients (n=58) with no significant difference in titre between the groups (Table 1). Two smokers and one non-smoker underwent thyroidectomy, two patients received radioiodine treatment.

All patients were treated with steroids (fluorocortolone 100 mg reduced by 10 mg every 4 days) for 6 weeks and, after that, with orbital irradiation (12 Gy). They were examined at the beginning of the study and after 6 weeks, 4.5, 7.5, and 12 months, respectively. Patients with mild TAO (clinical activity score <2), severe TAO (proptosis >24 mm, reduced visual acuity due to optic nerve compression), a TAO duration of more than 12 months, former anti-inflammatory treatment, and radioiodine therapy during the follow up period were excluded from the study.

All follow ups were carried out by the same investigator who assessed the following ophthalmological parameters:

1. Proptosis (mm) was measured, using the Hertel method.
2. The CAS was assessed as follows (we modified the scheme of Mourits): pain during eye movements (0–1), painful oppressive feeling on or behind the eye (0–1); lower (0–2) and...

See end of article for authors’ affiliations

Correspondence to:
Anja Eckstein, MD,
Department of Ophthalmology,
Hufelandstrasse 55,
45122 Germany;
anja.eckstein@uni-essen.de

Accepted for publication
7 October 2002

Background: In patients with Graves’ disease, smoking considerably increases the incidence and severity of thyroid associated ophthalmopathy (TAO). The authors sought to determine if smoking also influences the course of TAO during treatment, and the efficacy of therapy.

Methods: 41 smokers and 19 non-smokers with moderate untreated TAO were included in this prospective study. All patients were treated with steroids and, 6 weeks after the beginning of drug therapy, with orbital irradiation. Follow up was performed 1.5, 4.5, 7.5, and 12 months after the beginning of the study. Proptosis, clinical activity score (CAS), and motility were evaluated. The extent of smoking was derived from the concentration of the haemoglobin adduct N-2-hydroxyethylvaline (HEV), a parameter of long term smoking.

Results: There was no difference in the clinical manifestations of TAO between smokers and non-smokers at the beginning of treatment. However, CAS decreased (p<0.05) and motility improved (p<0.02) significantly faster and to a greater extent in non-smokers than smokers. Inverse correlations between the CAS decrease and the HEV levels observed 4.5 and 7.5 months after the beginning of treatment and between the improvement of motility and the HEV levels after 1.5, 4.5, and 7.5 months indicated a dose dependence. Mean HEV levels did not vary much during the follow up period and were significantly different in smokers (mean 5.4 (SD 2.7) µg/l) and non-smokers (mean 1.8 (1.3) µg/l; p<0.01).

Conclusion: Smoking influences the course of TAO during treatment in a dose dependent manner. The response to treatment is delayed and considerably poorer in smokers.

Patients and methods

Patients

The prospective study included 67 patients with active TAO of moderate severity (manifestation less than 12 months before the beginning of the study). Sixty patients completed a 1 year follow up period. The data of these patients were statistically evaluated. Five patients were lost during the follow up period owing to a lack of compliance or a change of residence. Two were excluded because of radioiodine therapy. Among the patients who completed the study, 41 were smokers (11 men and 30 women, mean age 46 (18–70) years) and 19 non-smokers (four men and 15 women, mean age 47 (30–69) years).

Thyroid status of the patients was mainly euthyroid with overt hyperthyroidism or hypothyroidism (because of overtreatment). Thyroidal function was not significantly different in smokers and non-smokers at the time of the initial presentation (Table 1) and during the course of the study (data not shown). TSH receptor antibodies were elevated in the majority of patients (n=58) with no significant difference in titre between the groups (Table 1). Two smokers and one non-smoker underwent thyroidectomy, two patients received radioiodine treatment.

All patients were treated with steroids (fluorocortolone 100 mg reduced by 10 mg every 4 days) for 6 weeks and, after that, with orbital irradiation (12 Gy). They were examined at the beginning of the study and after 6 weeks, 4.5, 7.5, and 12 months, respectively. Patients with mild TAO (clinical activity score <2), severe TAO (proptosis >24 mm, reduced visual acuity due to optic nerve compression), a TAO duration of more than 12 months, former anti-inflammatory treatment, and radioiodine therapy during the follow up period were excluded from the study.

All follow ups were carried out by the same investigator who assessed the following ophthalmological parameters:

1. Proptosis (mm) was measured, using the Hertel method.
2. The CAS was assessed as follows (we modified the scheme of Mourits): pain during eye movements (0–1), painful oppressive feeling on or behind the eye (0–1); lower (0–2) and...
upper eyelid oedema (0–2); conjunctival injection (0–1); conjunctival chemosis (0–1). This resulted in a maximal score of 8.

(3) Eye motility (score 0–3) was evaluated by measuring monocular excursion at the Goldmann perimeter: no impairment (0), impaired monocular elevation to 25°–35° and/or impaired monocular abduction to 35°–40° (1), impaired monocular elevation to 15°–24° and/or impaired monocular excursion at the Goldmann perimeter: no impairment (0), impaired monocular elevation to 25°–35° and/or impaired monocular abduction below 30° (3).

Improvement upon treatment was presumned, if the CAS was less than 2 (mean of both eyes), and/or proptosis was reduced by more than 2 mm (mean of both eyes), and/or motility improved from score 2 to 3 to score 0 or 1.

The characteristics of the patients at the beginning of the study are given in Table 1. All patients had a CAS >2 at the first visit. According to the patients, the first TAO symptoms (increase of lid width, a proptosis of eye balls, and oedema) appeared not earlier than 12 months before the initial examination. 27 patients had an impaired motility judged as grade 2 or 3.

Biochemical measurements
Biochemical parameters were determined by an immunometric assay (ACS, 180 Cheiron, Fernwald, Germany) with reference ranges for TSH of 0.3–4 mU/l, for serum FT4 of 10–25 pmol/l, for T4 of 58–154 nmol/l, and for T3 of 1.23–3.08 nmol/l. Patients receiving antithyroid drug treatment were regularly tested for euthyroidism. Patients with elevated TSH and/or FT3 were either treated with an adjusted dosage of levothyroxine or the doses of antithyroid drugs were reduced.

TSH receptor antibodies (TSHRab) were measured by the first generation TSH receptor assay (Brahms, Berlin, Germany).

**Determination of N-2-hydroxyethylvaline (HEV) as evidence of exposure to ethylene oxide**
Each visit included the quantitative analysis of the haemoglobin adduct N-2-hydroxyethylvaline (HEV). HEV was quantified as 1-(2-hydroxyethyl)-5-isopropyl-3-pentafluorophenyl-2-thiohydantoin derivative by gas chromatography/mass spectrometry (GC/MS) following isolation of the globin from haemolysed erythrocytes, derivatisation with pentafluorophenyl isothiocyanate, and cleavage from the protein by means of a modified Edman degradation procedure. A patient was considered a smoker if HEV levels were above 2.9 µg/l (smokers) and those of patients with levels below 2.9 µg/l (non-smokers) at the beginning of treatment were calculated with the unpaired two tailed t test. The response to treatment is presented via life table analysis according to Kaplan-Meier. The differences between smokers and non-smokers were tested with the log rank test 12 months after the beginning of the study. We calculated Spearman’s correlation coefficients for the relation between the improvement of symptoms and the HEV levels measured at the time of the consecutive examinations. The difference between the score at the beginning of the treatment and the score assessed in each follow up examination indicated the improvement of symptoms. A p<0.05 was considered significant.

**Medical ethics committee**
The study was approved by the medical ethics committee of the University of Essen, Germany.

<table>
<thead>
<tr>
<th>Statistical analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Differences between features of patients with HEV levels above 2.9 µg/l (smokers) and those of patients with levels below 2.9 µg/l (non-smokers) at the beginning of treatment were calculated with the unpaired two tailed t test. The response to treatment is presented via life table analysis according to Kaplan-Meier. The differences between smokers and non-smokers were tested with the log rank test 12 months after the beginning of the study. We calculated Spearman’s correlation coefficients for the relation between the improvement of symptoms and the HEV levels measured at the time of the consecutive examinations. The difference between the score at the beginning of the treatment and the score assessed in each follow up examination indicated the improvement of symptoms. A p&lt;0.05 was considered significant.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Medical ethics committee</th>
</tr>
</thead>
<tbody>
<tr>
<td>The study was approved by the medical ethics committee of the University of Essen, Germany.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>RESULTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical assessment before treatment</td>
</tr>
<tr>
<td>Owing to the exclusion of patients with mild and severe TAO, there was no significant difference between the clinical manifestations in smokers and non-smokers observed in the first examination, also, thyroid hormone status and antibody levels were similar in the two groups (Table 1).</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>HEV levels and smoking habits</th>
</tr>
</thead>
<tbody>
<tr>
<td>The HEV levels of smokers were significantly different from those of non-smokers in all examinations. However, the respective mean values in both groups did not vary much during the follow up period, indicating no change in smoking habits. The number of cigarettes smoked per day correlated positively with the HEV levels throughout the follow up period (r = 0.56–0.60; p&lt;0.001). Three non-smokers with HEV levels above 2.9 µg/l insisted on having quit smoking, but claimed to have continued substantial passive exposure to tobacco smoke.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Improvement of TAO symptoms in the course of treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Soft tissue injury (as judged by the CAS) responded best to the anti-inflammatory treatment, both in smokers and in non-smokers. In contrast, eye motility improved less favourably, and proptosis did not change significantly in both groups.</td>
</tr>
</tbody>
</table>

---

<table>
<thead>
<tr>
<th>Table 1 Baseline characteristics of the smokers (HEV &gt;2.9 µg/l) and non-smokers (HEV &lt;2.9 µg/l) obtained in the initial examination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feature</td>
</tr>
<tr>
<td>GD since (months)</td>
</tr>
<tr>
<td>TAO since (months)</td>
</tr>
<tr>
<td>Motility score</td>
</tr>
<tr>
<td>Proposis (mm)</td>
</tr>
<tr>
<td>HEV level (µg/l)</td>
</tr>
<tr>
<td>TSH (mU/l)</td>
</tr>
<tr>
<td>T3 (nmol/l)</td>
</tr>
<tr>
<td>T4 (nmol/l)</td>
</tr>
<tr>
<td>TSHRab (U/l)</td>
</tr>
</tbody>
</table>

GD = Graves’ hyperthyroidism, TAO = thyroid associated ophthalmopathy, CAS = clinical activity score, HEV = N2-hydroxyethylvaline, TSH = thyroid stimulating hormone, T4 = L-thyroxine, T3 = tri-iodothyronine, THS-R-Ab = TSH receptor antibodies. Median values, 5% and 95% confidence intervals are presented. |
The CAS (Fig 1A) has decreased to 1 or 0 in almost half of the non-smokers 4.5 months after the beginning of the study; the corresponding quota in smokers was 21%. After 12 months, the CAS has decreased to 1 or 0 in 74% of the non-smokers, but only in 55% of the smokers. The log rank test revealed a statistical difference between these two groups for the respective scores after 12 months (p<0.05).

The improvement of monocular elevation to 25° or more and/or monocular abduction to 35° or more in smokers and non-smokers is depicted in Figure 1B. While five non-smokers and 22 smokers showed an impaired motility score of 2 or 3 at the beginning of the study, the score of three non-smokers and four smokers has improved to score 0 or 1 a year later. The difference between the two groups was statistically significant (p<0.017).

Reduction of proptosis indicating improvement was rather poor in both groups. Three smokers and one non-smoker showed a reduction by more than 2 mm after 12 months. The difference between the two groups was not significant (Fig 1C).

**Table 2** Relation between improvement (CAS, motility, and proptosis) and HEV levels

<table>
<thead>
<tr>
<th>Months</th>
<th>CAS</th>
<th>Motility</th>
<th>Proptosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>-0.03</td>
<td>-0.04</td>
<td>-0.03</td>
</tr>
<tr>
<td>1.5</td>
<td>-0.16</td>
<td>-0.34</td>
<td>-0.03</td>
</tr>
<tr>
<td>4.5</td>
<td>-0.29</td>
<td>-0.33</td>
<td>-0.12</td>
</tr>
<tr>
<td>7.5</td>
<td>-0.30</td>
<td>-0.29</td>
<td>-0.08</td>
</tr>
<tr>
<td>12</td>
<td>-0.12</td>
<td>-0.23</td>
<td>-0.08</td>
</tr>
</tbody>
</table>

Significant correlations are indicated in bold.

**DISCUSSION**

This prospective study revealed a dependence of the therapeutic response to anti-inflammatory therapy on the extent of smoking in TAO patients only in the first months (1.5–7.5) after the beginning of treatment. No significant dose dependence was found for the outcome after 1 year, however, although Kaplan-Meier analysis still showed a significantly smaller reduction of clinical activity and a poorer improvement of motility in smokers than non-smokers at that time.

**Relation between HEV levels and the number of smoked cigarettes**

The use of cigarettes was reliably estimated by the quantification of HEV in haemoglobin. There was a significant correlation between the average number of cigarettes smoked per day according to the patients and the HEV levels. The correlation coefficients from \( r = 0.56 \) to 0.60 are almost identical to those obtained by Bailey,\(^{12}\) and only slightly below the respective coefficient of \( r = 0.63 \) calculated by Bono \(^{15}\) et al. Bono et al also considered the contribution of passive smoking, which might explain the higher value obtained in their investigation. Thus, the method employed in this study proved to be suitable to estimate the influence of smoking on the response to TAO therapy and to investigate the dependence of this response on the extent of smoking.

**Dependence of the improvement of TAO symptoms during treatment on the extent of smoking**

Soft tissue inflammation as expressed by the CAS responded best to the anti-inflammatory therapy: approximately two thirds of the patients showed a reduced CAS 1 year after the beginning of the study. The improvement of motility was only moderate (observed in one third of the patients) and a slight reduction of proptosis occurred only in a few patients. The significant correlation between the reduction of clinical activity and motility and the HEV levels 1.5–7.5 months after the beginning of drug therapy indicates a direct effect of smoking habits on the response to treatment. The more extensive the
use of cigarettes, the less favourable is the initial response to
treatment. A similar dose-effect relation has also been found
for the prevalence and severity of TAO. The fact that no such
relation was observed 12 months after the beginning of
treatment indicates that the response to treatment is only
delayed in smokers. These results are in agreement with those
of our previously conducted retrospective study in which the
final outcome of TAO was evaluated 280–1675 days after the
first examination. That former study had revealed that at the
first visit smokers showed oedema (p<0.02) and proptosis
(p<0.05) more often than non-smokers, whereas the prevalence
and severity of other eye symptoms did not differ in both
groups. In the course of treatment, a clear amelioration of
symptoms was observed in both groups independent of
smoking habits. Obviously, smoking did not adversely affect
the final outcome of treatment after the longer observation
period.

None of the smokers stopped smoking after having received
information on its detrimental effects on TAO. Therefore, it
was not possible to demonstrate that quitting smoking has
indeed a beneficial effect. Such an effect can be assumed,
however, if the relation between HEV levels and the improve-
ment of TAO is taken into consideration.

The pathological influence of smoking on thyroid function,
the immune system, and vascular and connective tissue has
been discussed in detail in former studies.  In summary, the determination of HEV is a suitable method
to estimate the intensity of smoking. Smokers with TAO
respond less favourably to steroids and to radiotherapy and
represent a group of patients suffering from a protracted
course of the disease in the first year after the initiation of
treatment. The effect of smoking on the initial response to
anti-inflammatory treatment is dose dependent, but it does
not influence the final outcome. Additional studies are
required to elucidate the prognostic relevance of quitting
smoking on the clinical course of Graves’ disease.

ACKNOWLEDGEMENTS
We thank Ms Katrin Rensing (Institute for Medical Informatics,
Biometry and Epidemiology at the University of Essen) for her expert
advice concerning the statistical evaluation of our data.

Presented in part at the 72nd Annual Meeting of the American
Thyroid Association, Palm Beach, FL, USA 1999.

Authors’ affiliations
A Eckstein, A W Rettenmeier, P Steuhl, J Esser, Department of
Ophthalmology, University of Essen, Germany
B Quadbeck, R Hoermann, K Mann, Department of Medicine, Division of
Endocrinology
G Mueller, Department of Hygiene and Occupational Medicine

REFERENCES
1 Hagg E, Asplund K. Is endocrine ophthalmopathy related to smoking?
2 Bartalena L, Martino E, Marocci C, et al. More on smoking habits and
3 Balass C, Stenszky V, Farid NR. Association between Graves’
ophthalmopathy and smoking. / Lancet 1990;335:1261–3.
5 Tellez M, Cooper J, Edmonds C. Graves’ ophthalmopathy in relation to
6 Prummel MF, Wiersinga WM. Smoking and risk of Graves’ disease.
JAMA 1993;269:479–482.
7 Winsa B, Mandal A, Karlsson FA. Graves’ disease, endocrine
8 Pfeilschifter J, Ziegler R. Smoking and endocrine
ophthalmopathy:impact of smoking severity and current vs lifetime
9 Bartalena L, Marocci C, Tanda ML, et al. Cigarette smoking and
treatment outcomes in Graves’ ophthalmopathy. Ann Intern Med
on the course of Graves’ ophthalmopathy under antiinflammatory
therapy. 71th Annual Meeting of the American Thyroid Association.
11 Farmer PB, Cordaro K, Autrup H. Monitoring human exposure to
12 Bailey E, Brooks AGF, Dollery CT, et al. Hydroxyethylvaline adduct
formation in haemoglobin as a biological monitor of cigarette smoke
as a guide in the management of patients with Graves’ ophthalmopathy.
14 Van Sittert NJ. N2-Cyanoethylvaline, N2-hydroxyethylvaline,
N-methylvaline (as evidence of exposure to acrylonitrile, ethylene oxide
as well as methylating agents). In: Angerer J, Schaller KH, eds (on behalf
of the Commission for the Investigation of Health Hazards of Chemical
Compounds in the Work Area of the Deutsche Forschungsgemeinschaft).
Analyses of hazardous substances in biological materials. Vol 5 VCH
15 Bono R, Vincenti M, Meineri V, et al. Formation of
N(2-hydroxyethyl)valine due to exposure to ethylene oxide via tobacco
16 Utiger RD. Effects of smoking on thyroid function. Eur J Endocrinol
17 Muller B, Zulewski H, Huber P, et al. Impaired action of thyroid hormone
associated with smoking in women with hypothyroidism. N Engl J Med
18 Metcalfe RA, Weetman AP. Stimulation of extracellular muscle fibroblasts
by cytokines and hypoxia: possible role in thyroid-associated
19 Schwartz J, Weiss ST. Cigarette smoking and peripheral blood
20 MclAllister-Sistilli CG, Caggula AR, et al. The effects of nicotine on the
21 Hofbauer LC, Mullberg T, Koening A, et al. Soluble interleukin-1
receptor antagonist serum levels in smokers and nonsmokers with Graves’
ophthalmopathy undergoing orbital radiotherapy. J Clin Endocrinol
Impact of smoking on the response to treatment of thyroid associated ophthalmopathy

A Eckstein, B Quadbeck, G Mueller, A W Rettenmeier, R Hoermann, K Mann, P Steuhl and J Esser

doi: 10.1136/bjo.87.6.773

Updated information and services can be found at:
http://bjo.bmj.com/content/87/6/773

These include:

References
This article cites 16 articles, 0 of which you can access for free at:
http://bjo.bmj.com/content/87/6/773#BIBL

Email alerting service
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Topic Collections
Articles on similar topics can be found in the following collections

Public health (479)
Orbit (60)

Notes

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/