



Is our recommendation for smoking cessation considered in patients with Graves disease and Graves orbitopathy?

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Abstract

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Aim: Smoking increases the risk of Graves' orbitopathy (GO) in patients with Graves' disease (GD). Therefore, smoking cessation should be recommended to all patients with GD. This study aimed to investigate whether smoking cessation recommendations were taken into account in patients with GD and whether there was a difference in terms of smoking cessation between those with and without GO.

Materials and Methods: Smoking status of the cases followed up with GD, who were active smokers when diagnosed, were questioned by telephone visit. The relationship of these data with the presence of GO was evaluated.

Results: 74 smokers with GD were included in the study. All patients were advised to quit smoking by their physicians. While the number of cigarettes was 20 (10-22)/day at the first visit, the current cigarette use was 7 (0-15)/day, ($p < 0.001$). Forty-nine (66.2%) of the patients had GO. It was found that 49% of patients with GO and 36% of those without GO quit smoking ($p = 0.28$). The decrease in number of cigarettes/day after physician's recommendation was significantly higher in patients with GO than patients without GO (-95.4% vs. -54.5%), ($p = 0.02$).

Conclusion: Although the importance of smoke cessation was emphasized in all patients with GD, we observed that smoking cessation advice was more followed in the GO group in our study. Explaining in detail that smoking in GD may worsen the course of the disease and impair the quality of life in the possible development of GO, may lead patients to consider smoking cessation recommendations more.



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Introduction

Graves' Disease (GD) is an autoimmune disease clinically characterized by hyperthyroidism, goiter, and extrathyroidal manifestations [1]. The onset of GD involves a deterioration of immune tolerance toward the thyroid through an autoimmune multifactorial process involving both endogenous and environmental factors [2]. One of the most important environmental risk factors is implicated as smoking [2,3].

Graves' orbitopathy (GO) is the most common extrathyroidal manifestation of GD [4]. Gender, high TSH receptor antibody levels, radioactive iodine treatment, thyroid hormone dysfunction (hypo/hyperthyroidism), selenium deficiency, stressful lifestyle, increase in intestinal dominance

of *Yersinia enterocolitica* and *Escherichia coli* are among the factors that play a role in the formation of GO [5]. Recently, the role of high cholesterol levels in the pathogenesis of GO has also been investigated [6]. In addition to all these, smoking is a preventable environmental risk factor that has a critical role in GO [3,4]. It has been reported that smoking was associated with a 2.6- and 3.1-fold increase in proptosis and diplopia, respectively. In addition, the risk increased with the number of cigarettes smoked per day [7]. Continuing to smoke despite the presence of GO is associated with poor response to GO therapy and poor clinical outcomes [8]. It has been shown that orbital fibroblasts have a remarkable response to cigarette smoke extract by increasing oxidative stress, increasing fibrosis-related gene expression, and especially by increasing levels of connective tissue growth factor and intracellular transforming growth factor- $\beta 1$ and interleukin- 1β in GO [9].

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The most up-to-date clinical guidelines for GO recommend smoking cessation with the highest level of evidence, both in GD without signs of orbitopathy and at all stages of GO, mild, moderate, and severe [4]. Although the recommendation to quit smoking is mentioned in all GO-related guidelines, there are very few field studies on this recommendation's clinical reflections and application status. In this study, we investigated whether smoking cessation recommendations were taken into account in patients with GD and whether there was a difference between those with and without GO.

Materials and Methods

Within the probability sampling method, it was planned to include patients with GD or GO who were smokers at the time of initial diagnosis followed up in the Department of Endocrinology and Ophthalmology. It was planned to include all cases accepted to participate in the study with a simple random sampling system from this probability sampling group. No face-to-face meetings were scheduled with the patients to reduce the risk of transmission due to the COVID-19 pandemic. By phone calls, a short questionnaire was administered to 74 patients who agreed to participate in the study among 104 patients who met the inclusion criteria. Demographic information, smoking status, treatment method of GD, and, if present, GO were questioned. Subjects who smoked at the time of diagnosis were asked whether they had received a doctor's advice on quitting smoking at the first visit. Afterwards, they were asked about their smoking status at last visit. The relationship of this information with demographic data was analyzed. This study had two hypotheses. The first hypothesis was that the number of cigarettes/per day decreased between the first and last visit after the physician's advice; the second hypothesis was that the rate of quitting or reducing smoking was higher in the GO group than in the without GO group. The first hypothesis was tested with the Wilcoxon test, and the second with the Mann-Whitney U test. This study was performed in line with the principles of the Declaration of Helsinki. Ethics approval was obtained from Local Ethics Committee (Gazi University Ethics Committee, Date 2021/No 123). Due to the risk of transmission of COVID-19, informed consent was obtained with the approval of the information form sent to the mobile phone within the knowledge of the ethics committee.

Statistical analysis

IBM SPSS Statistics 22.0 (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY, IBM Corp.) computer package program was used. The conformity of continuous variables to normal distribution was evaluated by Shapiro-Wilk test, while the homogeneity of variance was evaluated by Levene's test. T-test or Mann-Whitney U test was used to compare the two independent groups according to the normality and homogeneity of the data. Wilcoxon test was used to analyze dependent groups that are not normally distributed. Chi-square tests were used for categorical variables among independent groups. In descriptive statistics, categorical variables were presented as numbers and percentages and, mean and

standard deviation (Mean±SD) for normally distributed variables, median and 25-75% for not normally distributed variables were given. As a result of the normality analysis, it was determined that the data of the continuous variables, except age, were not normally distributed.

This study recorded the number of cigarettes/day used by the patients at the first and last visit. After the physician's advice, the analysis of the change in the number of cigarettes/day in all groups was done with the Wilcoxon test. By comparing the number of cigarettes/day used at the first and last visit, the patients were categorized as quit smoking, decreased the number of cigarettes/day, remained the same, and increased the number of cigarettes/day. In addition, the percentage of reduction in smoking was calculated using the formula $\frac{(\text{Number of cigarettes/day at first visit} - \text{last visit})}{(\text{Number of cigarettes/day at first visit})} \times 100$. This percentage of reduction in smoking was compared between the GO and without GO groups with Mann-Whitney U test. The statistical significance level was accepted as $p < 0.05$.

Results

Seventy-four active smokers with GD at the time of diagnosis were included in the study. Follow-up time was 6 ± 3 years. The mean age of the patients was 48.0 ± 10.9 years, and 46 (62.2%) of them were women. Forty-two (56.8%) of the patients used only antithyroid drugs, 24 (32.4%) had a thyroidectomy, and 8 (10.8%) were given radioactive iodine (RAI) treatment. Forty-nine (66.2%) of the patients had GO. Of the GO cases, 25 (71.4%) had mild, 14 (28.6%) had moderate, and 10 (20.4%) had severe orbitopathy. While 23 (46.9%) of GO cases were followed without treatment, 12 (24.5%) had local treatments, 10 (20.4%) had IV methylprednisolone treatment, and 4 (8.2%) had decompression surgery. As shown in Table 1, there was no difference between patients with GO and without GO in terms of gender, age, and amount of smoking at admission ($p > 0.005$).

We found that all patients were advised to quit smoking by their doctor at the first visit. While the number of cigarettes used by the participants at the first visit was 20 (10-22)/day, the current number of cigarettes was 7 (0-15)/day. There was a statistically significant decrease in smoking after the physician's advice ($p < 0.001$). It was observed that 33 (44.6%) patients quit smoking, 23 (31.1%) decreased the number of cigarettes/day, 16 (21.6%) used the same amount, and 2 patients increased the number of cigarettes/day.

Table 1. Characteristics of smokers with and without Graves orbitopathy.

Parameter	GO (n:49)	Without GO (n:25)	p
Age (years)	49.0±11.1	45.4±10.3	0.210
Gender (Women) n(%)	29 (59.2)	17 (68.0)	0.613
Cigarettes/day	20 (10-23)	15 (5-20)	0.169
Cessation smoking n(%)	24 (49)	9 (36)	0.28
Reduction in the number of cigarettes (%)	95.4	54.5	0.020

GO: Graves Orbitopathy.

Reduction in the number of cigarettes/day after physician's advice was significantly higher in patients with GO compared to patients without GO (20 (10-23) to 2 (0-15)/day; 95.4% decrease vs. 15 (5-20) to 5 (0-15)/day; 54.5% decrease, $p=0.02$), (Table 1). It was observed that 24 (49.0%) patients with GO quit smoking, 17 (34.7%) decreased the number of cigarettes/day, 7 (14.3%) remained the same, and one patient had an increase in the number of cigarettes/day. In the patients without GO, 9 (36.0%) patients quit smoking, 6 (24.0%) decreased the number of cigarettes/day, 9 (36.0%) remained the same, and one patient had an increase in the number of cigarettes/day. It was found that 24 (49%) of patients with GO and 9 (36%) of those without GO quit smoking ($p=0.28$). No relationship was found between the change in the amount of cigarettes and age, gender, and the severity of orbitopathy ($p>0.05$).

Discussion

In this study, we found that both patients with GD and GO gave importance to their doctors' recommendations to quit smoking. Although there was no difference between smoking cessation rates between the patients with GO and without GO, there was a greater reduction in the number of cigarettes in people with GO. This is an impressive result as we know that every cigarette increases the risk of orbitopathy [10]. Smoking is the most important preventable risk factor for GO, affecting vision and self-perception [11]. It is predicted that preventing smoking would reduce the occurrence of GO by 28.1% in patients with GD [12].

In a multicenter study, there was no difference between the knowledge levels about thyroid-related eye disease in patients with GD and GO, although both groups had higher knowledge than healthy controls. However, it was observed that both groups did not know the effects of smoking on orbitopathy [13]. Therefore, it is extremely important to explain the harms of smoking to patients with GD and GO at the visits and patients should be guided to quit smoking. Smoking cessation advice for patients with GD is included in all clinical guidelines with the most robust evidence to prevent GO onset, prevent its progression when GO does occur, and improve treatment response [4]. Despite this, only 30% of clinicians advised smoking cessation to patients with GO, according to a 2002 study [14]. It is impressive that all patients were advised to quit smoking at the first visit by their doctor in our study. This may be due to a better understanding of the effect of smoking on orbitopathy over the years and raising the awareness of doctors on this issue. In addition, the cooperation of endocrinology and ophthalmology is an important factor that facilitates GO management [15]. We think that the smoking cessation advice was given to every patient, and the high rate of smoking reduction in patients with GO in our clinic may be related to the fact that we have a combined endocrinology and ophthalmology clinic for GO, as suggested by EUGOGO [4].

Palomero et al. assessed the effect of oral counseling for smoking cessation in patients with GO, and found that 42% of the cases quit smoking, and 30% decreased their number of cigarettes/day. Patients in their study who quit

smoking generally had active and severe GO and received more support from their relatives and friends [16]. In our study, the proportion of patients who quit and reduced smoking in the GO group is similar to the study of Palomero et al. [16]. Although the smoking cessation rate is expected to be higher in patients with severe disease, we did not find a relationship between disease severity and smoking reduction rate in our study. We think that even mild orbitopathy affects the patient's emotional state and persuades the patient to reduce smoking. It might be helpful to explain the risk of developing orbitopathy to patients with GD by using case images in several consecutive visits.

In a study of Schatz et al., patients with GO who received at least one tobacco counseling session quit smoking at a higher rate than those who did not [17]. None of our patients received professional support to quit smoking, all of them stated that they tried to quit smoking on their own or with the support of their relatives. Although all patients were advised to quit smoking, referral to a professional smoking cessation center would have given better smoking cessation rates in our study. Additional advice to quit smoking should have been made, such as referring patients to group-based counseling or smoking cessation centers who could not quit smoking at the follow-up visits.

Our study differs from other studies in that it included cases with GO and compared these cases in terms of smoking cessation to the patients without GO. GO causes negative self-image and impaired visual function, anxiety and significant deterioration in the quality of life [18]. It has been shown that the quality of life is improved after decompression and strabismus surgery in patients with GO [19]. GO-related deterioration in the quality of life may have led to greater enthusiasm to GO patients for quitting smoking that causes GO. In our study, the difference in smoking reduction percentages between the two groups may be due to the fact that patients without GO did not experience the negative aspects of the thyroid-related eye problems. The severity of orbitopathy, of which smoking is one of the biggest factors, may be explained to patients without GO through visual atlases. Therefore, it may be easier for them to quit smoking when they understand the importance of smoking in this disease.

Conclusion

This study had two critical endpoints. Firstly, for those with GD, the the clinicians' advice to quit smoking was effective with or without GO. Secondly, although the importance of quitting smoking was emphasized in all patients with GD in our study, it was observed that smoking cessation advice was more followed in patients with GO. We think that GO patients have given more attention to smoking cessation recommendations due to the concerns about vision and self-image. Explaining in detail that smoking may worsen the course of the disease in GD without orbitopathy and that the quality of life may deteriorate in the possible development of GO may lead to more significant consideration of the physician's recommendations for smoke cessation. We also care about emphasizing the importance of getting counselling for smoking reduction.

Ethical approval

Ethics approval was obtained from Local Ethics Committee (Gazi University Ethics Committee, Date 2021/No 123).

Conflicts of interest

The authors have no conflict of interest to declare

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