ORIGINAL ARTICLE

# Efficacy and safety of radioiodine therapy for mild Graves ophthalmopathy depending on cigarette consumption: a 6-month follow-up

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**KEY WORDS**

cotinine, Graves disease, Graves ophthalmopathy, radioiodine, smoking

**ABSTRACT**

**INTRODUCTION** Graves ophthalmopathy (GO) is an autoimmune disease associated with Graves disease. Its treatment is largely dependent on the severity and activity of ocular lesions. Particular attention should be given to radioiodine (RAI) therapy. Although its use is a valuable therapeutic option for hyperthyroidism, it may be followed by worsening of GO.

**OBJECTIVES** The aim of the present study was to analyze how the severity of nicotine addiction affects the response to RAI treatment in patients with GO.

**PATIENTS AND METHODS** A total of 106 patients (58 smokers and 48 nonsmokers) with mild GO treated with 800 MBq of RAI were included to the study. We assessed the serum levels of thyroid-stimulating hormone (TSH), thyroid hormones, autoantibodies against thyroperoxidase, thyroglobulin, and TSH receptor (TSHR-Abs), as well as urinary cotinine levels and severity of ophthalmopathy. Analyses were conducted at baseline (before RAI treatment) and 2 and 6 months after the therapy.

**RESULTS** Significant differences in serum levels of TSHR-Abs were found between nonsmokers and smokers at 2 and 6 months after RAI therapy, whereas there were no differences at baseline. In smokers, there were significant differences in the severity of ophthalmopathy and the concentration of serum TSHR-Abs assessed at baseline and at 6 months of follow-up. Six months after RAI therapy, 46.2% of smokers and 4.3% of nonsmokers ($P < 0.001$) progressed from mild to moderate GO.

**CONCLUSIONS** High urinary cotinine levels in smokers were associated with the deterioration of ocular lesions after RAI treatment. A high dose of RAI did not induce an exacerbation of GO in nonsmokers who were administered oral steroid prophylaxis.

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Received: May 13, 2016.
Revision accepted: August 5, 2016.
Published online: August 18, 2016.
Conflict of interest: none declared.
Pol Arch Med Wewn. 2016; 126 (10): 746-753
doi:10.20452/pamw.3505


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**INTRODUCTION** Graves ophthalmopathy (GO) is an ophthalmologic manifestation of Graves disease. The therapy of GO is largely dependent on the severity and activity of ocular lesions.[1] Additionally, the severity of GO is influenced both by endogenous factors, such as sex, genetic characteristics, or pregnancy, and by exogenous factors, such as thyroid dysfunction, cigarette smoking, or $^{131}$I (RAI) therapy.[2-6] Particular attention should be given to RAI therapy, which is a valuable method of treatment of hyperthyroidism, but may be followed by worsening of GO.[3,7,8] The therapy can induce increased production of thyroid-stimulating hormone (TSH) receptor antibodies (TSHR-Abs)

**TABLE 1** Basic demographic, biochemical, thyroid, and eye-specific differences at baseline between smoking and nonsmoking patients

| Parameter | Nonsmokers (n = 48) | Smokers (n = 58) | *P* value |
|---|---|---|---|
| age, y | 39.2 ±1.14 | 37.2 ±0.97 | NS |
| women | 43 (89.6) | 50 (86.2) | NS |
| TSH, μIU/ml | 0.06 ±0.01 | 0.05 ±0.009 | NS |
| $FT_4$, pmol/l | 25.3 ±0.3 | 27.0 (0.35) | NS |
| $FT_3$, pmol/l | 8.8 ±0.36 | 10.3 ±0.44 | NS (0.07) |
| Tg-Abs, IU/ml | 218 ±85.6 | 246.1 ±171.8 | NS |
| TPO-Abs, IU/ml | 232.8 ±140.2 | 246 ±145.3 | NS |
| TSHR-Abs, IU/l | 11.7 ±6.3 | 15.9 ±6.2 | NS |
| urinary cotinine, ng/ml | 3.8 ±1.6 | 371.9 ±48.8 | <0.001 |
| thyroid volume, ml | 26.7 ±0.9 | 31.3 ±1.1 | 0.02 |
| correct vision acuity | 44 (91.7) | 45 (77.6) | NS (0.06) |
| RAI uptake, % | | | |
| after 5 h | 26.7 ±7.4 | 27.5 ±8.4 | NS |
| after 24 h | 55.0 ±17.1 | 53.5 ±7.7 | NS |
| NOSPECS grade | | | |
| 1 | 35 (72.9) | 28 (48.3) | 0.001 |
| 2 | 3 (6.3) | 19 (32.8) | |
| 3 | 10 (20.8) | 6 (10.3) | |
| 4 | 0 | 5 (8.6) | |
| exophthalmos, mm | | | |
| right eye | 17.3 ±0.4 | 19.9 ±0.3 | <0.001 |
| left eye | 17.0 ±0.3 | 20.2 ±0.3 | <0.001 |
| max. exophtalamos | 18.1 ±0.3 | 20.7 ±0.3 | <0.001 |
| max. retraction, mm | | | |
| 0 | 14 (29.2) | 6 (10.3) | 0.003 |
| 1 | 31 (64.6) | 36 (62.1) | |
| 2 | 3 (6.3) | 16 (27.6) | |
| CAS, points | | | |
| 2 | 25 (52.1) | 14 (24.1) | 0.003 |
| 3 | 23 (47.9) | 44 (75.9) | |
| incorrect eye mobility, mm | | | |
| right eye | 3 (6.3) | 17 (29.3) | 0.003 |
| left eye | 3 (6.3) | 17 (29.3) | 0.003 |
| any eye | 3 (6.3) | 17 (29.3) | 0.003 |

Data are presented as mean ± standard error of the mean or number (percentage) of patients.

Abbreviations: CAS, clinical activity score; $FT_3$, free triiodothyronine; $FT_4$, free thyroxine; NS, nonsignificant; RAI, radioiodine; Tg-Abs, autoantibodies against thyroglobulin; TPO-Abs, autoantibodies against thyroperoxidase; TSH, thyroid-stimulating hormone; TSHR-Abs, autoantibodies against TSH receptor

and, subsequently, eye injury. To avoid these effects, glucocorticoid prophylaxis should be considered.[9] However, it is still unknown what dose of radioiodine (RAI) should be used to avoid a relapse or deterioration of GO.

The aim of the present study was to analyze how the severity of cigarette smoking, assessed with the cotinine concentration in urine, influences the course of GO in patients treated with RAI.

## PATIENTS AND METHODS

**Patients** Patients with GO treated in the outpatient clinic of the Department of Endocrinology, Metabolism and Internal Medicine, Poznan University of Medical Science, Poznań, Poland, between March 2014 and October 2014, were included in the study. Serum levels of TSH, thyroid hormones, and thyroid autoantibodies, as well as urinary levels of cotinine were assessed before the therapy and at 2 and 6 months after the therapy. All patients were examined by the same experienced ophthalmologist (KK-R) before the therapy and at 6 months. The inclusion criteria were inactive, mild, or moderate-to-severe GO and treatment with 800 MBq (22 mCi) of RAI. The exclusion criteria were active and moderate-to-severe GO, sight-threatening GO, lack of compliance (patients who did not present at the follow-up visit at 2 or 6 months), and refusal to undergo RAI treatment.

The study was approved by the Ethical Committee of the Poznan University of Medical Sciences. Written informed consent was obtained from all participants.

**Antithyroid, radioiodine, and corticosteroid treatment** Before RAI therapy, 95 patients were treated with methimazole and 11—with propylthiouracil. Treatment with antithyroid drugs was discontinued at least 24 hours prior to RAI therapy. In 24% of the patients, the drugs were reintroduced at least 7 days after RAI therapy. All patients were prescribed a prophylactic therapy with oral glucocorticoids, namely, prednisone (0.3–0.5 mg/kg bw/d) initiated after RAI therapy and gradually tapered down and withdrawn after 6 weeks.[11,12]

**Ophthalmological examination** An ophthalmological examination was performed according to the European Group On Graves' Orbitopathy recommendations and its Polish adaptation.[17,18] Activity of GO was assessed using the clinical activity score (CAS)[13,14] (spontaneous retrobulbar pain, pain on attempted up or down gaze, redness of the eyelids, redness of the conjunctiva, swelling of the eyelids, inflammation of the caruncle and/or pica, and conjuctival edema). GO was classified as active when the CAS was 3/7 or higher. The NOSPECS scale was used to assess the severity of GO[15,16] (N, no signs or symptoms; O, only signs, no symptoms; S, soft tissue involvement; P, proptosis; E, extraocular muscle involvement; C, corneal involvement; S, sight loss).

Worsening of GO in the ophthalmologic examination indicated the disease progression.

**Urinary cotinine levels** Urinary cotinine [(5S)-1-methyl-5-(3-pyridyl)pyrrolidin-2-one)] is a nicotine metabolite that reflects exposure to tobacco smoke. Patients were divided into 2 groups based on urinary cotinine levels. Nonsmokers and individuals not exposed to environmental tobacco smoke had cotinine levels of 5 ng/ml in urine/mg creatinine; individuals exposed to this factor had from 5 to 50 ng of cotinine in urine/mg creatinine (passive exposure); and active smokers had more than 50 ng of cotinine in urine/mg

**TABLE 2** Serum levels of thyroid parameters, urinary level of cotinine, and thyroid volume in nonsmoking and smoking patients with mild Graves ophthalmopathy

| Group | TSH, μU/ml | $FT_4$, pmol/l | $FT_3$, pmol/l | TPO-Abs, IU/ml | Tg-Abs, IU/ml | TSHR-Abs, IU/l | Cotinine, ng/ml | Thyroid volume, ml |
|---|---|---|---|---|---|---|---|---|
| at 2 months | | | | | | | | |
| nonsmokers | 0.56 ±1.49 | 17.2 ±3.7 | 6.5 ±1.2 | 336.2 ±223.4 | 276.5 ±154.2 | 14.0 ±7.6 | 2.6 ±7.9 | 25.6 ±4.6 |
| smokers | 0.2 ±0.9 | 20.0 ±5.3 | 7.9 ±3.7 | 399.0 ±236.6 | 345.8 ±193.4 | 23.5 ±8.5 | 473.4 ±362.6 | 27.9 ±8.1 |
| *P* value | NS | NS | NS | NS | NS | <0.001 | <0.0001 | NS |
| at 6 months | | | | | | | | |
| nonsmokers | 1.98 ±2.58 | 22.3 ±2.9 | 4.5 ±0.8 | 312.9 ±223.7 | 278.5 ±154.0 | 12.0 ±5.2 | 4.1 ±13.3 | 23.2 ±5.0 |
| smokers | 2.1 ±2.3 | 17.2 ±3.0 | 5.3 ±1.9 | 315.4 ±193.0 | 271.5 ±125.4 | 26.6 ±8.9 | 599.5 ±387.5 | 26.6 ±7.4 |
| *P* value | NS | NS | NS | NS | NS | <0.001 | <0.0001 | NS |

Data are expressed as mean ± SD.

Reference ranges are as follows: $FT_4$, 11.5–21.5 pmol/l; $FT_3$, 3.9–6.8 pmol/l; TSH, 0.27–4.2 μU/ml; TSHR-Abs, <2 IU/l; Tg-Abs, <115 IU/ml; and TPO-Abs, <35 IU/ml. The urinary concentration of cotinine: nonsmokers (<5 ng/ml), passive smokers (5–50 ng/ml), and smokers (>50 ng/ml). Thyroid volume was measured by ultrasonography (reference range, 18–25 ml).

Abbreviations: see TABLE 1

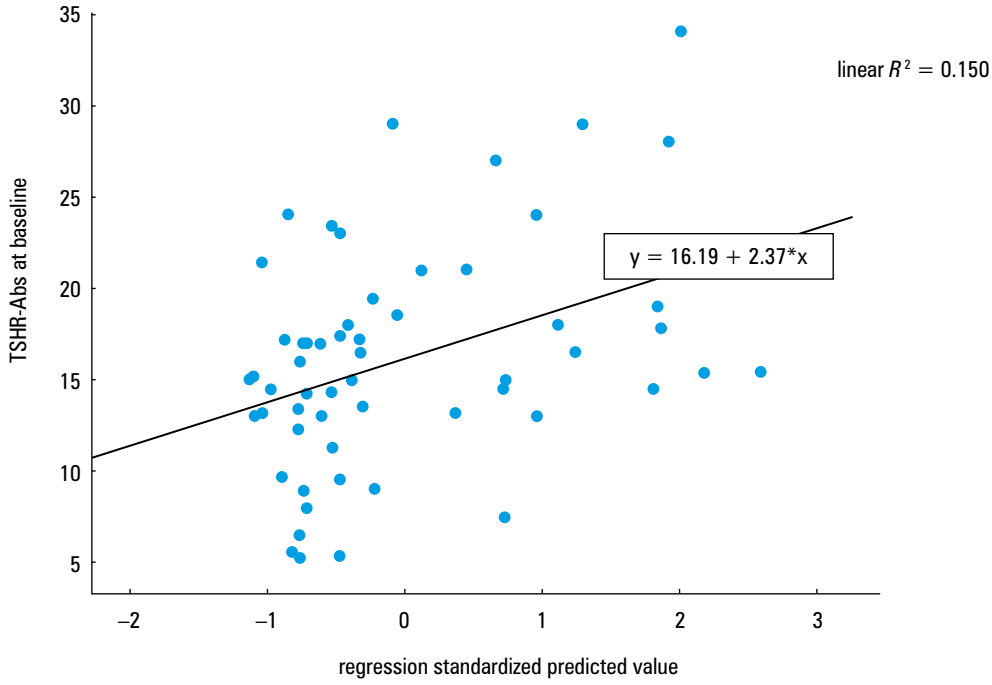


**FIGURE 1** Regression standardized predicted value of autoantibodies to thyroid-stimulating hormone receptor (TSHR-Abs) in smokers

creatinine (light smokers, 50–500 ng/ml; moderate smokers, 500–2500 ng/ml; and heavy smokers, >2500 ng/ml).[19]

Cotinine was dissolved in methanol to create a standardized solution (Wao Pure Chemicals, Osaka, Japan and Sigma Chemical St Louis, Missouri, United States), which was then added to urine (nonsmokers) and distilled water to prepare a range of concentrations: 2.1, 27.6, 55.2, 82.8, 110, 138, 276, 552, 828, 1100, and 1380 ng/ml for cotinine.

A gas chromatograph (GC-14B, Kyoto, Japan) equipped with a capillary column and flame thermionic sensor was used for the measurement of urinary cotinine levels. The injection port and detector temperature was 260°C. The column temperature was constant at 150°C for 2 minutes, then increased to 260°C at a rate of 10°C per minute, and was held constant for 2 minutes as the final temperature. Nitrogen at 15 kPa was the carrier gas.

One milliliter of urine was added to 0.1 ml of 12 μg/ml of carbinoxamine maleate in methanol and 1 ml of 1M carbonate buffer (pH 9.7). The upper aqueous phase was aspirated and disposed of, while the remaining organic phase was transferred to a new single-use tube. The organic phase was re-extracted with 1 ml of 0.1N HCl and vigorously vortexed for 30 seconds. The resulting aqueous phase was transferred to a new disposable tube and 1-ml carbonate buffer, added, and re-extracted using 4-ml dichloromethane vortexed for 30 seconds. The organic phase was mixed with 20 μl of isoamyl alcohol and dichloromethane, along with succeeding evaporation under a mild flow of nitrogen in a heated block at 35°C. The remaining alcohol solution (1 μl) was then injected into the gas chromatograph.

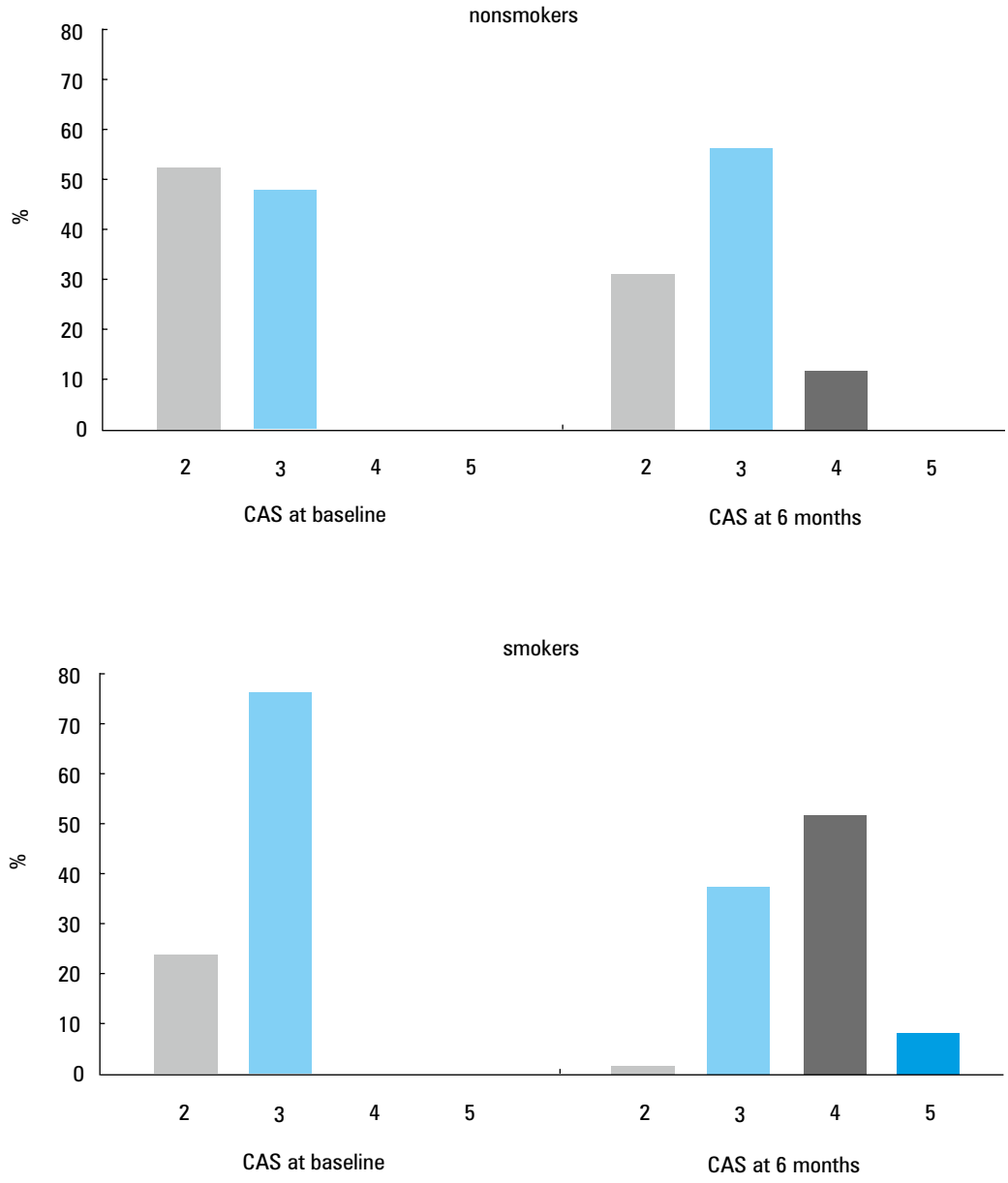


**FIGURE 2** Distribution of clinical activity score (CAS) in nonsmokers and smokers at baseline and at 6 months of follow-up ($P < 0.001$)

**Assays** The levels of TSH, free thyroxine ($FT_4$) and free triiodothyronine ($FT_3$) were measured using the electrochemiluminescence technique in Cobas E 601 (reference ranges: TSH, 0.27–4.2 mU/l; $FT_4$, 11.5–21.5 pmol/l; and $FT_3$, 3.9–6.8 pmol/l). The TSHR-Abs titer was estimated using second-generation antibodies (RIA-2 Dynotest TRAK human, BRAHMS Diagnostica GmbH, Berlin, Germany) (reference range <2 IU/ml). Autoantibodies against thyroglobulin (Tg-Abs) and autoantibodies against thyroid peroxidase (TPO-Abs) were measured with a radioimmunoassay (reference ranges <115 IU/ml and <35 IU/ml, respectively).

**Sonography, radioiodine uptake, and scintigraphy** A thyroid ultrasound (The Aloka IPC-1530, Tokyo, Japan) performed by a 7.5-MHz linear transducer was used to assess thyroid volume, and the ellipsoid model (width × length × thickness × 0.52 for each lobe) was used for calculation.[19] The RAI uptake was measured in every patient before the therapy, and 5 and 24 hours after the administration of 2 MBq (54 μCi) of $^{131}I$. All patients received the same therapeutic activity of 800 MBq of RAI (TABLE 1).[10]

**Statistical analysis** Statistical analyses were performed using Statistica 10 software by StatSoft (Tulsa, Oklahoma, United States). A $P$ value of less than 0.05 was considered significant. Categorical dichotomous data were analyzed using the McNemar test, and continuous data were analyzed using either the paired-samples $t$ test or repeated measures analysis of variance (ANOVA). Data were presented with means and standard error of the mean or percentages.

**RESULTS** Of 126 subjects, 106 were eligible for the inclusion in the study (93 women, 13 men). The reasons for ineligibility (n = 20, 15.8%) included inadequate information (n = 11, 8.7%) and incomplete laboratory data (n = 9, 7.1%).

The baseline characteristics of the patients are shown in TABLE 1. The results of thyroid status

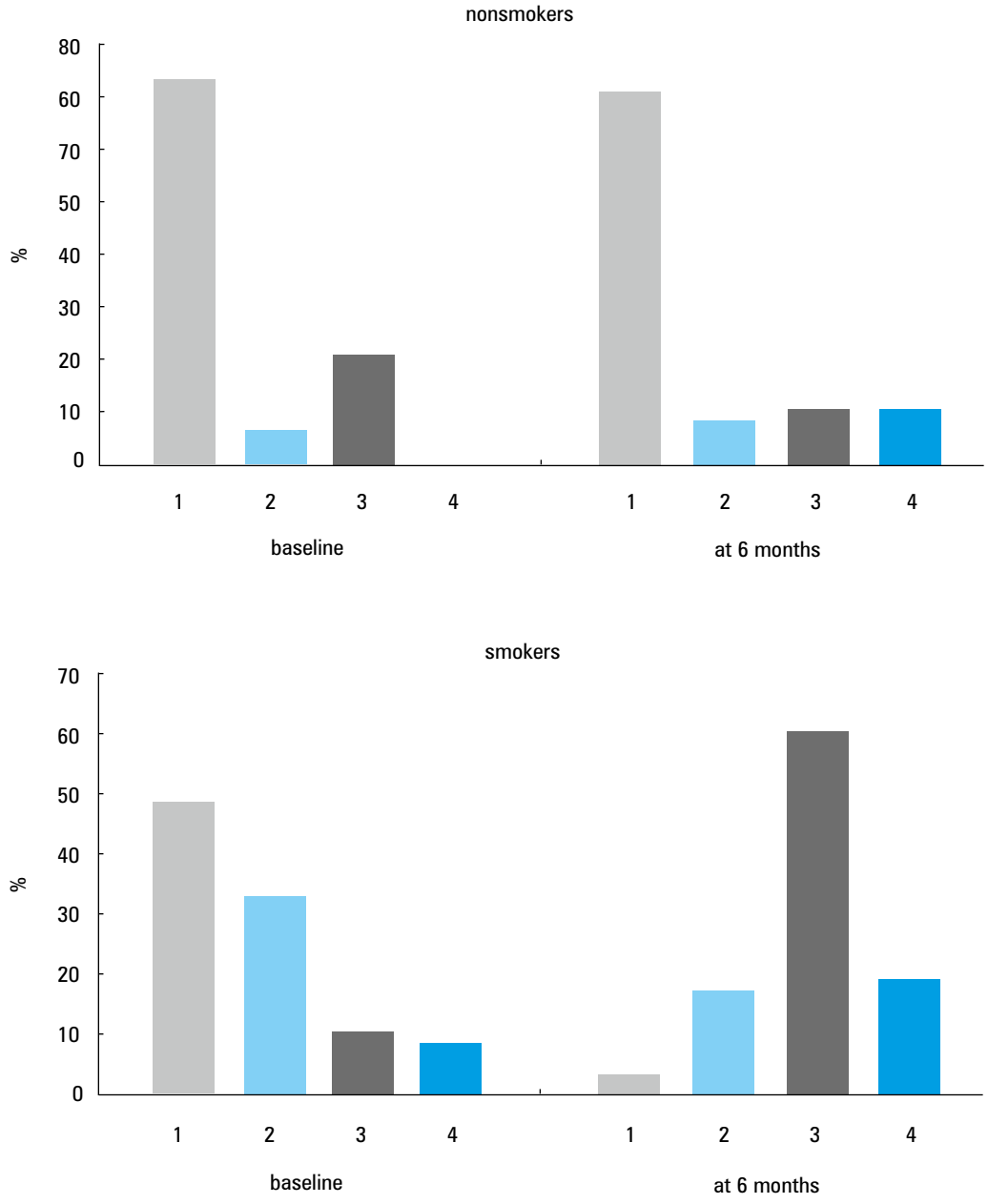


**FIGURE 3** Distribution of the NOSPECS grade in nonsmokers and smokers at baseline and at 6 months of follow-up ($P < 0.001$)

assessment 2 and 6 months after RAI therapy are presented in TABLE 2.

**Thyroid function** At the end of follow-up, 46 smoking patients (79.3%) were successfully treated (persistent hypothyroidism or euthyroidism), 5 (8.6%) developed subclinical hyperthyroidism, and 7 (12.1%) remained symptomatically hyperthyroid. Among nonsmokers, 8 (16.7%) had persistent hypothyroidism, 34 (70.8%) were euthyroid, and 6 (12.5%) had recurrent thyrotoxicosis.

**Serum levels of TSHR-Abs, TPO-Abs, and Tg-Abs autoantibodies** The levels of autoantibodies, TSH, and thyroid hormones during follow-up are shown in TABLE 1 (at baseline) and TABLE 2. Among smoking patients, a significant increase in TSHR-Abs levels following RAI therapy was observed ($P < 0.001$). FIGURE 1 shows regression standardized predicted value of TSHR-Abs in smoking patients. In the group of nonsmokers, there were no significant differences in the serum level of TSHR-Abs at baseline or during follow-up ($P > 0.05$).

**Serum levels of TSHR-Abs, urinary levels of cotinine, and clinical activity score** The urinary levels of cotinine before RAI therapy and at 6 months of follow-up differed significantly between nonsmokers and smokers ($P < 0.001$). In smoking patients, there were also significant differences in urinary cotinine levels and serum TSHR-Abs levels between baseline values and those at 6 months ($P < 0.001$). In addition, significant differences were also observed in this group of patients in the activity of opthlamopathy (CAS), and serum TSHR-Ab levels at baseline and during follow-up ($P < 0.001$, ANOVA). There was also a significant correlation between urinary cotinine levels and CAS at baseline and at 6 months ($P < 0.001$). No significant associations were observed in the nonsmoking group.

**Ophthalmological lesions (activity and severity measures)** The CAS was significantly higher in smokers at baseline ($P = 0.003$, TABLE 1) and 6 months after RAI therapy ($P = 0.0001$, FIGURE 2) compared with nonsmokers. None of the patients in the nonsmoking group had conjunctival edema. Spontaneous retrobulbar pain was common among smokers and deteriorated after 6 months, while it was not observed in the nonsmoking group.

There were significant differences between smokers and nonsmokers in terms of the incidence of proptosis at baseline and at 6 months of follow-up (NOSPECS 3, $P < 0.001$). Moreover, there were significant differences between the groups after 6 months of follow-up in terms of the worsening of diplopia (NOSPECS 4, $P < 0.05$) (FIGURE 3). Similar changes were observed in lid aperture (NOSPECS 1) and visual acuity, which were increased in smokers as compared with nonsmokers ($P < 0.01$). A decrease in visual acuity due to corneal disorder or neuropathy of optic nerve was not observed. We also analyzed retraction and exophthalmos (TABLE 1). In none of the cases, corneal involvement, punctuate keratopathy, ulcer (NOSPEC 5), or optic nerve involvement (NOSPECS 6) were observed.

Deterioration of ophthalmopathy was observed at 6 months of follow-up in 27 smokers (46.2%) and 2 nonsmokers (4.3%), who were subsequently upstaged to moderate-to-severe GO.

## DISCUSSION

In the present study, the effect of nicotine consumption on the efficacy and safety of RAI therapy for mild GO was assessed. Smoking and nonsmoking patients were examined by an ophthalmologist before RAI therapy and 6 months after the therapy. The dose of 800 MBq of RAI was applied in both groups. Smoking habits reported by the patients were analyzed with regards to urinary cotinine concentrations, the measuring of which is a gold standard for assessing the total nicotine exposure irrespective of direct cigarette smoking.

The association between RAI therapy and worsening of GO has been investigated in numerous studies.[17,21-24] RAI therapy has been proved to directly affect the deterioration and development of ophthalmopathy in 15% to 39% of patients.[16,20,21] Randomized case-control trials confirmed a significantly higher risk of deterioration of ophthalmopathy after RAI treatment in comparison with antithyroid drugs.[21-23]

The results of our study clearly demonstrate that RAI treatment is associated with ocular lesions and worsening of GO, particularly in smokers. According to our results as well as those of Kobe et al,[10] RAI therapy is not always followed by progression of ophthalmic abnormalities when a high dose of RAI (800 MBq) is applied. In our study, the worsening of ophthalmopathy was present in less than 5% of nonsmoking patients. In order to reduce the risk of worsening of GO, all patients received oral glucocorticoid prophylaxis (30 mg/d). Such treatment was shown to have a potential protective effect.[6,8,11]

It is difficult to explain such good effects of the high dose of RAI combined with oral glucocorticoids. It might be speculated that a small dose of RAI leads to a prolonged worsening of autoimmunity against TSHR-Abs, as compared to high doses of RAI (800 MBq). Our findings may have practical implications. Considering the fact that more beneficial effects can be obtained by using a high dose of RAI, it is unnecessary to perform the complex calculation of an appropriate dose.

According to our results and numerous previous findings,[25-28] RAI therapy is often followed by persistent hypothyroidism, which can result in worsening of opthalmopathy. Therefore, to prevent the exacerbation of ocular lesions, it is particularly important to prevent the development of hypothyroidism by thyroid function monitoring after RAI treatment and, if necessary, early administration of L-thyroxine.[25,26]

A major problem in the management of smoking patients is how to cure smoking addiction. High values of cotinine as a biomarker for the exposure to tobacco smoke directly show how smoking influences the RAI therapy in terms of ocular lesions. Our study has confirmed a significant association between urinary cotinine levels and increased CAS in smokers ($P < 0.001$), whereas no such association was reported for the nonsmoking group. Cotinine is used to determine whether a patient has consumed a cigarette in the past several days (up to 1 week).[19] Furthermore, cotinine is a valuable marker in cases when patients' self-reports on their smoking habits are not completely accurate.

To our knowledge, our study is the first to show a relationship between RAI therapy and consumption of cigarettes and exacerbation of GO. We only performed a preliminary study before, using a similar methodology but a different and almost twice smaller group of patients.[29]

The effect of cigarette smoking on TPO-Abs and Tg-Abs still remains controversial. According to some other studies, cigarette smoking is associated with a lower prevalence of TPO-Abs and Tg-Abs.[30,31] Belin et al[30] established a negative correlation between the cotinine concentration and the serum level of TPO-Abs and Tg-Abs in smokers.

In conclusion, ocular lesions occur with much greater intensity in smokers with high urinary cotinine levels. A high dose of RAI does not induce exacerbation of ophthalmopathy in nonsmokers.

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ARTYKUŁ ORYGINALNY

# Skuteczność i bezpieczeństwo leczenia jodem promieniotwórczym łagodnej oftalmopatii tarczycowej w zależności od konsumpcji papierosów – półroczna obserwacja

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**SŁOWA KLUCZOWE**

choroba Gravesa, jod promieniotwórczy, kotynina, oftalmopatia Gravesa, palenie

**STRESZCZENIE**

**WPROWADZENIE** Oftalmopatia tarczycowa (*Graves ophthalmopathy* – GO) to choroba autoimmunologiczna związana z chorobą Gravesa. Jej leczenie w dużym stopniu zależy od ciężkości i aktywności zmian ocznych. Szczególnej uwagi wymaga kwestia leczenia jodem promieniotwórczym (*radioiodine* – RAI). Choć jego podanie stanowi cenną metodę leczenia nadczynności tarczycy, może pociągnąć za sobą pogorszenie GO.

**CELE** Celem badania było wskazanie, w jaki sposób ciężkość nikotynizmu wpływa na efekty terapii RAI u pacjentów z GO.

**PACJENCI I METODY** Bo badania włączono 106 pacjentów (58 palących i 48 niepalących) z łagodną GO leczonych RAI w dawce 800 MBq. U badanych oceniono w surowicy stężenia hormonu tyreotropowego (*thyroid-stimulating hormone* – TSH), hormonów tarczycy, przeciwciał przeciwko tyreoperoksydazie (TPO-Abs), tyreoglobulinie (Tg-Abs) i receptorowi dla TSH (TSHR-Abs), poziom kotyniny w moczu, a także stopień zaawansowania oftalmopatii. Badania przeprowadzono w momencie włączenia do badania (przed podaniem RAI) oraz 2 i 6 miesięcy po terapii.

**WYNIKI** Wykazano istotne różnice w stężeniu TSHR-Abs u osób palących i niepalących w 2. i 6. miesiącu po terapii RAI, nie występowały one natomiast przed podaniem RAI. U palących wystąpiły istotne różnice w zakresie zaawansowania oftalmopatii i stężenia TSHR-Abs ocenionego przed podaniem RAI oraz 6 miesięcy po jego podaniu. Sześć miesięcy po terapii RAI u 46,2% palących i 4,3% niepalących ($p < 0{,}001$) poziom zaawansowania oftalmopatii zwiększył się z łagodnego do umiarkowanego.

**WNIOSKI** Wysokie stężenie kotyniny w moczu u osób palących wiązało się z pogorszeniem zmian ocznych po terapii RAI. Wysoka dawka RAI nie indukowała nasilenia GO u osób niepalących przy zastosowaniu doustnej osłony sterydowej.

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Praca wpłynęła: 13.05.2016.
Przyjęta do druku: 05.08.2016.
Publikacja *online*: 18.08.2016.
Nie zgłoszono sprzeczności interesów.
Pol Arch Med Wewn. 2016; 126 (10): 746-753
doi:10.20452/pamw.3505


*AC i KK-R miały równy udział w tworzeniu pracy.