

Original article

Cigarette Smoking Has no Impact on the Effect of Radioiodine Therapy in Patients with Graves Disease

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SUMMARY

Presently, there is very little data on the impact of nicotine and other components of tobacco smoking on the outcome of radioiodine therapy (RIT) in Graves' disease (GD). Thus, this study was aimed to analyze a possible impact of cigarette smoking on the effect of radioiodine therapy in the patients with Graves' disease.

The study included 31 patients (16 smokers and 15 non-smokers) with GD, aged from 22 to 73 years, who were treated with a single dose of iodine-131 sodium iodide (¹³¹I-NaI) and subjected to a 12-month follow-up, thereafter. Patients were treated with antithyroid drugs (ATDs) before RIT and described very intense stressful events occurring prior to diagnosing Graves' hyperthyroidism. A successful response to RIT was defined as euthyroidism and subclinical or clinical hypothyroidism, while an unsuccessful response was defined as persistent hyperthyroidism.

Comparison of age (47.4±9.41 vs. 49.5±13.8 years, p=0.628) at the time of RIT, applied activity of ¹³¹I-NaI (372±78.4 vs. 363±43.7 MBq, p=0.675), and duration of ATDs therapy (3.47±3.33 vs. 4.94±5.62 years, p=0.387) between smokers and non-smokers showed no significant difference. The cumulative incidence of successful response to therapy in smokers and non-smokers was 31.2 vs. 46.7% (p<0.05), 50.0 vs. 60.0% (p>0.05), 56.2 vs. 60.0% (p>0.05), and 56.2 vs. 66.7% (p>0.05) after 3, 6, 9 and 12 months, respectively.

The results showed that cigarette smoking has no impact on the effect of radioiodine therapy after twelve-month period in patients who had experienced stressful events before the occurrence of Graves' disease. However, patients with smoking habits achieved successful response later than non-smokers.

Key words: Graves' disease, radioiodine therapy, cigarette smoking

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INTRODUCTION

Graves' disease (GD) is a very frequent autoimmune disorder of the thyroid manifested by one or more of the following features which can occur together or independently: hyperthyroidism, ophthalmopathy and dermatopathy. The initiation and progression of disease involves a complex interaction of multiple genetic and environmental exogenous or endogenous factors required to trigger thyroid autoimmunity (1). This results in the presence of circulating thyroid stimulating hormone (TSH) receptor protein autoantibodies (TRAb) which bind to those receptors on the thyroid membranes and stimulate thyroid gland causing an excessive production and secretion of thyroid hormones and clinical manifestation of hyperthyroidism. The protein antigens are T cell dependent antigens, therefore, CD4⁺ T cells, most likely, play an important role because they provide the necessary help for autoantibody production (2).

It is recognized and widely accepted that some environmental factors such as iodine intake, infection, stressful events or smoking may precipitate autoimmunity and GD in genetically predisposed individuals (3, 4). The interplay between genetic susceptibility and environmental factors is related to genetic polymorphisms which normally occur in the general population.

Cigarette smoking is a well recognized risk factor for the development of Graves' hyperthyroidism (GH) and especially for Graves' ophthalmopathy (GO) (5-9). Despite this fact, the biological mechanism responsible for the diverse effect of smoking and numerous components in tobacco (more than 4000) on the thyroid gland remains largely unknown. It is supposed that smoking might augment immunologic responsiveness to whatever factor initiates Graves' disease or, on the other hand, it might impair restoration of tolerance to thyroid autoantigens (7).

Although the autoimmune mechanisms are responsible for GD development, the therapeutic approach is directed toward controlling hyperthyroidism. Radioiodine therapy (RIT) is an option in most cases if disease is not controlled or recurs after initial antithyroid drugs (ATDs) therapy or if side effects of medication occurred. The purpose of this therapy is to destroy sufficient thyroid tissue and to cure hyperthyroidism by accepting hypothyroidism and lifetime thyroxine replacement therapy. Many factors

may have influence on radioiodine therapeutic efficacy such as treatment with ATDs, applied dose of radioiodine, age, gender, thyroid volume, thyroid hormone levels, thyroid radioiodine uptake, stressful events prior to development of GD or cigarette smoking (10-14).

AIM

Currently, there is very little data on the impact of nicotine and other components of tobacco smoking on the outcome of RIT in GD. Therefore, the aim of this study was to analyze a possible impact of cigarette smoking on the effect of radioiodine therapy in the patients with Graves' disease. Additionally, the possible influence of other factors on radioiodine therapy outcome, such as gender, age, duration of ATDs treatment and ophthalmopathy was also analyzed.

PATIENTS AND METHODS

Patients

This retrospective study included 31 hyperthyroid patients with GD (23 women), aged from 22 to 73 years, who were treated with a single dose of iodine-131 sodium iodide (¹³¹I-NaI) and subjected to a follow-up within 12-month period thereafter. All patients were treated with ATDs before RIT and described very intense stressful events prior to setting a diagnosis of Graves' disease. Those events were different and the most frequently mentioned were problems in the family (9 patients) and illness or death of a family member (6 patients). Problems at work, personal diseases or injuries and exile were reported by 4, 4 and 2 patients, respectively. One patient mentioned the occurrence of an intense joyful event, while the other stressful events were thieves attack, delivery of twins, military exercise and in two cases the presence of multiple consecutive different stressful events. According to the smoking status, patients were divided into two groups: I smokers (16 patients who smoked cigarettes before, at the moment and after RIT), and II non-smokers (15 patients). The possible impact of gender, age, duration of ATDs therapy and ophthalmopathy on radioiodine therapy response was analyzed in all patients, as well as in smokers and non-smokers.

Methods

A written consent was obtained from each patient before the initiation of radioiodine therapy. Patients also received detailed information about the procedure, possible outcome and safety.

Antithyroid drugs were stopped three days before RIT and if TSH and thyroid hormones serum levels showed severe hyperthyroidism, then ATDs were administered again two weeks after. Beta-adrenergic antagonists and sedative drugs were used to control the symptoms of hyperthyroidism during ATDs withdrawal. To achieve higher absorption, food intake was stopped three hours before and after radioiodine ingestion. Radioiodine dose was determined according to the goiter size, e.g., 296 MBq, 370 MBq, and 444 MBq for gradus 0 (none, gland impalpable or normal size), gradus 1 (small, thyroid palpably enlarged but not visible) and gradus 2 (medium or large, palpable and visible goiter), respectively.

The therapy outcome was assessed every third month till twelve months after radioiodine application by serum TSH and thyroid hormones levels as well as a clinical evaluation. A successful response to RIT was defined as euthyroidism and subclinical or clinical hypothyroidism, while an unsuccessful response was defined as persistent hyperthyroidism.

Ultrasensitive TSH was measured by fluoroimmunoassay (LKB-Wallac, Finland) (reference interval 0.170-4.05 mU/l, working range 0.010-100). Total serum thyroxine (tT₄) and triiodothyronine (tT₃) concentrations were also measured by fluoroimmunoassay method (reference interval for tT₄ and tT₃: 69.0-141 nmol/l and 1.3-2.5 nmol/l, working range 22.1-313 and 0.55-10.5)

Statistical analysis

Data are shown as mean±standard deviation and percentage. Independent samples Student's t-test or chi-square test was used to assess the differences in patients' groups' results and among variables in the same group. Significance was inferred at p value of 0.05. A statistical analysis was performed using the Statistical Package for the Social Sciences version 12 (SPSS Inc, Chicago IL, USA).

RESULTS

The comparison of age and TRAb values at the time of RIT, administered activity of ¹³¹I-NaI, as well as the duration of ATDs therapy before RIT between smokers and non-smokers with Graves' disease showed no significant differences (Table 1).

Table 1. Age and TRAb values at the time of RIT, duration of ATDs therapy before RIT and activity of ¹³¹I-NaI in smokers and non-smokers with Graves' disease

	Smokers (mean±SD)	Non-smokers (mean±SD)	p value
Age (years)	47.4±9.41	49.5±13.8	0.628
TRAb (U/l)	2.52±0.99	2.84±1.16	0.653
ATDs therapy (years)	3.47±3.33	4.94±5.62	0.387
Dose of ¹³¹ I-NaI (MBq)	372±78.4	363±43.7	0.675

Overall, after 12 months of follow-up, 19 (61.3%) patients were cured with one dose of radioiodine. As seen in Table 2, the cumulative incidence of successful response to therapy in two groups of patients was similar in three-month-follow-up intervals with an exception of the third month when a poorer response was noted in smokers.

Table 2. Cumulative incidence of successful response to radioiodine in smokers and non-smokers with Graves' disease

Month	Smokers (%)	Non-smokers (%)	p value
3 th	31.2	46.7	<0.05
6 th	50.0	60.0	>0.05
9 th	56.2	60.0	>0.05
12 th	56.2	66.7	>0.05

In patients with Graves's disease, independently of their smoking habit, the rate of successful response to radioiodine therapy at the end of the study was significantly higher in females than in males and in patients treated by ATDs up to two years than those treated more than two years before radioiodine therapy (Table 3). On the contrary, ophthalmopathy and age of patients (≤ 45 years or > 45 years) were not influential on the therapy outcome.

Table 3. Influence of gender, age, ophthalmopathy and duration of ATDs therapy on successful response twelve months after RIT in all studied patients with Graves's disease

	Successful response (%)	p value
female vs. male	65.2 vs. 50.0	<0.05
≤ 45 years vs. > 45 years	66.7 vs. 57.9	>0.05
presence vs. absence of GO*	64.7 vs. 57.1	>0.05
≤ 2 yr ATDs vs. > 2 yr ATDs	78.6 vs. 47.1	<0.0001

*GO – Graves' ophthalmopathy

As seen in Table 4, females, younger patients (≤ 45 years), patients without ophthalmopathy and those treated over two years with ATDs who did not smoke considerably responded better to RIT than those who smoked cigarettes.

Table 4. Influence of gender, age, ophthalmopathy and duration of ATDs therapy on successful response twelve months after RIT in smokers and non-smokers with Graves' disease

	Smokers %	Non-smokers %	p value
Female	58.3	72.8	<0.05
Male	50.0	50.0	>0.05
≤ 45 years	50.0	83.3	<0.0001
> 45 years	60.0	55.6	>0.05
presence of GO	63.6	66.7	>0.05
absence of GO	40.0	66.7	<0.0001
≤ 2 y ATD	75.0	83.3	>0.05
> 2 y ATD	7.5	55.6	<0.01

Before radioiodine treatment, there were significantly more patients with than without ophthalmopathy among smokers, while in the group of non-smokers significantly higher percentage of patients had no ophthalmopathy (Figure 1). The exacerbation or progression of ophthalmopathy was not observed during the follow-up period after RIT.

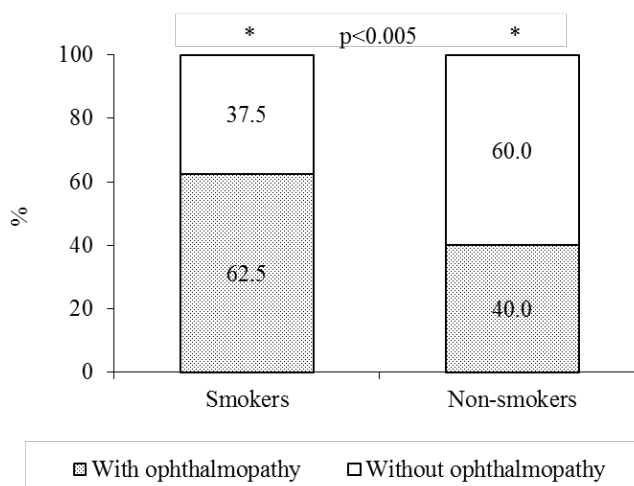


Figure 1. Incidence of ophthalmopathy in smokers and non-smokers with Graves' disease before radioiodine treatment with ophthalmopathy vs. without ophthalmopathy: * $p < 0.05$; between smokers and non-smokers: $p < 0.005$

DISCUSSION

Oral administration of $^{131}\text{I-NaI}$ has been used for the treatment of hyperthyroidism since 1941. The treatment is based on the selective accumulation of $^{131}\text{I-NaI}$ in the thyroid tissue, wherein the beta minus radiation emitted by the ^{131}I causes the inflammatory reaction and cell necrosis with consequent atrophy and fibrosis as final processes. The range of beta particles in glandular tissue is about 0.80 mm, so that the irradiation of adjacent structures is minimal. This form of treatment is safe, painless, effective and economical.

Successful outcome of radioiodine therapy is defined as elimination of hyperthyroidism, i.e., the achievement of euthyroid or hypothyroid state. Euthyroid state presents an ideal outcome, but it is limited to insufficient number of patients with Graves' disease. Hypothyroidism is accepted as a favorable effect, because it could be easily controlled by levo-thyroxine (15). Thus, the only unfavorable

outcome should be persistent hyperthyroidism that requires re-application of higher dose of radioiodine.

The outcome of radioiodine treatment of Graves' hyperthyroidism is unpredictable, but it has been proven that many factors can have an impact (10-14). In this study, patients who smoked cigarettes and those who had not smoked were approximately of the same age and had approximately the same serum levels of TRAb at the time of RIT. Also, they were pre-treated with thyrostatic medications during a similar period of time and received a similar dose of radioiodine. In view of the fact that between two groups of patients no differences were found in these variables, we were able to assess better the effect of smoking on the final result of RIT in patients who had experienced stressful events before the occurrence of Graves' disease.

The results of this study showed that cigarette smoking was not significantly influential factor of failed response to radioiodine therapy. Approximately the same percentage of cured patients was demonstrated after six and nine months after RIT, as well as at the end of the observation period in smokers (56.2%) and non-smokers (66.7%) who reported a stressful event before the diagnosis of Graves' disease. The only exception is shown after three months when the poorer response was noted in patients with smoking behavior.

Effect of smoking on the outcome of radioiodine therapy was not much studied in literature. To our knowledge, only one study has previously shown that smoking was not associated with poorer outcome of RIT in Graves' disease (13). Namely, Dora et al. (13) found no significant differences in respect to smoking status, age, sex, pre-treatment with methimazole, thyroid volume, and thyroid hormones levels in patients treated with 200 μ Ci/ml and 250 μ Ci/ml of radioiodine corrected for 24 hour thyroid uptake. After twelve months, 9 smokers (47%) and 10 non-smokers (53%) were cured. In our study, carried out with approximately the same number of smokers and non-smokers, the incidence of both cured smokers and non-smokers was slightly higher. This could perhaps be explained by the fact that all patients of the current study experienced emotional stress before the development of hyperthyroidism, which in turn, contributed to the earlier achievement of

hypothyroidism (12), i.e., greater cumulative incidence of successful responses to RIT.

The interrelationship of GD and smoking has been shown in numerous studies (7-9). However, it is unknown how smoking acts on radioiodine therapy response in GH because of insufficient studies. On the other hand, cigarette smoking may represent clinically useful predictor of the risk of recurrence in patients with Graves' hyperthyroidism treated with ATDs (16). The effect of cigarette smoke varies between different effects of components of tobacco including alkaloids, gases and carcinogens which may affect thyroid function and autoimmunity. It has been revealed that cytochrome P4501A1 (CYP1A1) enzymes play a key role at phase I metabolism of polycyclic aromatic hydrocarbons and other toxic components of cigarette smoke which are subsequently detoxified by phase II enzymes such as glutathione S-transferases (GST). When these enzymes are not able to avoid cellular damages, the TP53 gene plays an important role by recognizing and repairing DNA injuries (17, 18). GST is subjected to regulation by several hormones including thyroid hormones. Both T₃ and T₄ have been shown to reduce GST activity, so we assumed that an increase in these hormones may exert an influence on the outcome of both ATDs and radioiodine therapy.

It is described in literature that stress experienced before the onset of overt clinical symptoms of Graves' disease emphasizes the development of hypothyroidism after radioiodine treatment (12). Stewart et al. (12) showed that patients in which the stress initiated the symptoms of GD became hypothyroid earlier, compared to those where the stress was not specified in their history (hypothyroidism is reached in 50% of patients under stress within 12 months, but not until 36 months for the non-stress group, $p=0.01$). Patients in two groups were of similar age and sex and received a similar dose of radioiodine. After ten years, only 5% of patients from the stress group remained euthyroid, compared to 17% from the non-stress group. On the basis of these results, the authors hypothesized that the increased autoimmune reaction against the thyroid gland acts synergistically with radiation and led to an earlier development of hypothyroidism in patients who

underwent stress. The radioiodine therapy could cause thyroid follicular disruption with the release or new exposure of thyroid autoantigens, especially TSH receptors antigens, although this has never been presented directly. Indirect evidence of this phenomenon, which occurs after radioiodine treatment, includes T cell activation, prolonged elevation of TRAb and a transient increase in serum pro- and anti-inflammatory cytokines (19).

Our results that successful response to RIT independently of smoking behavior was significantly higher in patients treated by ATDs less than two years than in those treated over two years and in females than males are in accordance with the findings of other studies (14, 20). We also showed that age of patients and ophthalmopathy were not influential on RIT outcome in the whole population. It is in opposition with the results of Allahabadia et al. (14). In that study, younger patients (<40 years) had a lower successful response to RIT than patients over 40 yr old (68.9 vs. 79.3%). It is possible that this difference is a result of generally younger population in their study (the mean age of females and males was 38.4 and 38.6 years). This fact suggests that unknown age-related factors and/or hormonal changes may have influence on effectiveness of RIT. Poorer effects of radioiodine in younger persons may be in relation to the severity of hyperthyroidisms at diagnosis of Graves' disease, with higher iodine turnover and its shorter biological half-life in the thyroid gland.

Comparison of variables between smokers and non-smokers showed somewhat different results than in the whole population of patients in the present study. Namely, younger patients (≤ 45 years), patients without ophthalmopathy and those treated over two years with ATDs that belong to non-smokers' group better responded to radioiodine treatment than patients who smoked. Currently, there are no data on the impact of these variables on RIT outcome in smokers, so we could not compare our results.

In this study, 62.5% of smokers and only 40.0% of non-smokers ($p < 0.005$) had thyroid-associated ophthalmopathy, which is in accordance with other studies (5, 6). Smoking is the strongest

modifiable risk factor for developing Graves' ophthalmopathy, and the severity of ophthalmopathy is related to the current number of cigarettes smoked per day (5). The mechanism by which smoking affects GO is not known. It has been supposed that the formation of superoxide radicals and tissue hypoxia may be involved. Superoxide radicals can induce orbital fibroblasts to proliferate and cigarette smoke either contains or can generate a variety of oxidants and free radicals (21). Partial hypoxia induced by cigarette smoke components increases the synthesis of glycosaminoglycans by retrobulbar fibroblasts (22), thereby exacerbating the extraocular muscle swelling. It is also supposed that smoking might alter the structure of the TSH receptor making it more immunogenic in a way that leads to the production of TRAb that reacts strongly with retro-orbital tissue (7). Although smoking increases the risk of progression of ophthalmopathy after radioiodine therapy (3), we did not detect an exacerbation or progression of thyroid eye disease after RIT.

CONCLUSION

The results of this study showed that cigarette smoking has no impact on the effect of radioiodine therapy after twelve-month period in patients who had experienced stressful events before the occurrence of Graves' disease. However, patients with smoking behavior achieved later successful response than non-smokers. Younger non-smokers (≤ 45 years), females, as well as those without ophthalmopathy and treated over two years with ATDs better responded to radioiodine treatment than patients who smoked. The exacerbation or progression of thyroid-associated ophthalmopathy was not detected in both smokers and non-smokers.

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Pušenje cigareta nema uticaj na ishod radiojodne terapije kod bolesnika sa Grejvsovom bolešću

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SAŽETAK

Za sada ima veoma malo podataka u literaturi o uticaju nikotina i drugih komponenti duvanskog dima na ishod radiojodne terapije (RIT) kod Grejvsove bolesti (GB). U skladu sa tim, cilj ove studije bio je da se analizira mogući uticaj pušenja cigareta na efekat RIT kod bolesnika sa Grejvsovom bolešću.

Efekat terapije jednom dozom radiojoda (¹³¹I-NaI) procenjen je nakon 12 meseci kod 31 bolesnika sa GB (16 pušača i 15 nepušača), od 22 do 73 godine. Bolesnici su lečeni antitiroidnim lekovima (ATL) pre RIT. Stresni događaji bili su prisutni kod svih ispitanika pre postavljanja dijagnoze Grejvsovog hipertiroidizma. Uspešan odgovor na RIT je definisan kao eutiroidizam i klinički ili subklinički hipotiroidizam, a neuspešan odgovor kao perzistentni hipertiroidizam.

Komparacijom starosnog doba (47,4±9,41 vs. 49,5±13,8 godina; p=0,628) u vreme RIT, aplikovane aktivnosti ¹³¹I-NaI (372±78,4 vs. 363±43,7 MBq, p=0,675) i trajanja kontinuirane terapije ATL pre RIT (3,47±3,33 vs. 4,94±5,62 godina; p=0,387) nisu uočene statistički značajne razlike između pušača i nepušača. Kumulativna incidencija uspešnog odgovora na RIT kod pušača i nepušača nakon 3, 6, 9 i 12 meseci bila je: 31,2 vs. 46,7% (p<0,05), 50,0 vs. 60,0% (p>0,05), 56,2 vs. 60,0% (p>0,05) i 56,2 vs. 66,7% (p>0,05).

Rezultati su pokazali da pušenje cigareta nije uticalo na efekat radiojodne terapije nakon 12 meseci kod bolesnika koji su naveli stresni događaj pre pojave Grejvsove bolesti. Međutim, uočeno je da se kod pušača kasnije postiže uspešan odgovor na RIT nego kod nepušača

Ključne reči: Grejvsova bolest, radiojodna terapija, pušenje cigareta