The influence of radioiodine therapy on ocular changes and their relation to urine cotinine level in patients with Graves’ Ophthalmopathy

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Key words: radioiodine therapy; Graves’ hyperthyroidism; glucocorticoids; ocular changes

Abstract

OBJECTIVES: Radioiodine therapy (RIT) is frequently used as the definitive treatment in patients with Graves’ hyperthyroidism when remission is not achieved with anti-thyroid drugs (ATDs). In this observational study, we intended to examine whether the use of high doses of radioiodine (RAI) [22 mCi (814 MBq)] with prophylaxis of oral glucocorticoids (oGCS) does not exacerbate Graves ophthalmopathy (GO) in smokers and non-smokers, especially regards to the urine cotinine and ocular changes before and after RIT.

PATIENTS AND METHODS: The studied group consisted of 26 smokers, aged 28–61 years and 25 non-smoker patients, aged 21–54 years, respectively. The patients were enrolled to RAI after one-year of ineffective ATDs treatment. Criterion for inclusion in the study were patients with mild GO with hyperthyroidism at diagnosis based on the severity (NOSPECTS) and activity (CAS) scale. All the patients were subjected to RIT with oGCS prophylaxis and evaluated prospectively during a one-year follow-up. The ophthalmological examination was performed at various stages of RIT: initial pre-radioiodine administration, at the time of treatment 6, and 12 months after RAI. The present study is unique, because the urine cotinine measurement was employed to detect nicotine exposure, also in regard to smoking intensity.

RESULTS: In smokers, the values of serum TPO-Abs were statistically significant in the second and six month (p<0.05) and in the second and after one
CONCLUSIONS: 1) ablative RIT dose with prophylactic oral prednisone is a safe treatment in both smokers and non-smokers with mild GO; 2) The post hoc analysis showed that urinary level of cotinine can be very helpful in the assessment of exacerbation of ophthalmological clinical symptoms before and after RIT particularly in smokers.

Abbreviations:

ft4  - free tetraiodothyroxine
ft3  - free triiodothyronine
GO  - Graves' Ophthalmopathy
RAI  - radioiodine
RAIU  - radioiodine uptake
RIT  - radioiodine therapy
TSH  - thyrotropin
TSHR-Abs  - autoantibodies to the thyrotropin receptor
Tg-Abs  - thyroglobulin autoantibodies
TPO-Abs  - thyroperoxidase autoantibodies

INTRODUCTION

Radioiodine therapy (RIT) is frequently used as the definitive treatment in patients with Graves’ hyperthyroidism when remission is not achieved with antithyroid drugs (ATDs) (Singer et al. 1995; Cooper 1996). Other currently accepted risk factors for deterioration of ophthalmologic symptoms in patients undergoing RIT comprise a high anti-TSH receptor antibodies (TSHR-Abs) and high serum concentration of free triiodothyronine (FT3) (Sisson et al. 2008; Tallstedt et al 1992; Bartalena & Tanda 2009; Bartalena et al. 1998a; Laurberg 2008). Furthermore, a minority of patients presenting moderate to severe Graves’ Ophthalmopathy (GO) after-RIT requires treatment, while majority of them develop only mild and transitory progression (Prummel et al. 1990). The causative relation between radioiodine (RAI) and progression of GO has been demonstrated in several studies (Bonnema et al. 2002; Tallstedt et al. 1992; Bartalena & Tanda 2009; Kung et al. 1994; Vannucchi et al. 2009), but some authors reported lack of association (Gorman 1995; Prummel et al. 1990). In addition to RIT, tobacco smoking is presenting a significant influence on the course of orbitopathy as well (Bartalena et al. 2011; Marocci et al. 1999; Rasmussen et al. 2000; Prummel et al. 1997; Tallstedt et al. 1992; Bartalena et al. 2008; Bartalena 2002; Bartalena et al.1989; Bartalena et al. 1998b; Hagg & Asplund 1987; Hagedus et al. 2004; Kendler et al. 1993; Meberg & Marstein 1986; O’Hare & Georghegan 1993; Oliveira et al. 2009; Tomer & Davies 2003).

Cotinine is a metabolite of nicotine and is used as a biomarker for exposure to tobacco smoke (Triggle 1996). This marker detects smokers, even after several days (up to one week) after cigarette consumption (Florek et al. 2006). Furthermore, it cotinine is a valuable marker, in cases when patients do not always tell the doctors truth referring to their smoking. Hitherto, the studies presenting relationship between RIT and smoking in regard to exacerbation of GO including measurement of urine cotinine level were not reported.

In this observational study, we intended to examine whether the use of high doses of radioiodine (RAI) [22 mCi (814 MBq)] with prophylaxis of oral glucocorticoids (oGCS) does not exacerbate Graves ophthalmopathy (GO) in smokers and non-smokers, especially regarding to the urine level cotinine and ocular changes before and after RIT.

PATIENTS AND METHODS

Criterion for study inclusion was mild GO in patient with accompanying hyperthyroidism at diagnosis. Hyperthyroidism was elucidated on the basis of severity (NOSPECS) and activity (CAS) scale. The studied group consisted of 26 smokers (23 women and 3 men) aged 28–61 years, and 25 non-smoker patients (21 women and 4 men) aged 21–54 years, respectively (Table 1). The patients in two groups did not reveal significant discrepancy referring to the age at diagnosis, gender, median duration of GO. Patients were enrolled to RAI after one year of ineffective antithyroid drugs (ATDs) treatment. Among the non-smokers, only in one case ATDs could not be used due to granulocytopenia and transaminasemia after combined pegylated IFN-α (Peginterferon alfa-2a, Pegasys) and Ribavirin (Copegus) therapy for chronic hepatitis C (CHC). In this particular case, the administration of IFN-α influenced the development of GO (Czarnywojtek et al. 2012).

The diagnosis of GO was established on the basis of following criteria: goiter on palpation and in thyroid ultrasound, proptosis or exophthalmos assessed with an
follows: TSH: 0.27–4.2 μIU/ml, fT4: 11.5–21.5 pmol/L, antibody concentrations for our laboratory were as formed at various stages of RIT: initial pre-radioiodine administration, at the time of treatment, and then subsequently after 6 and 12 months after RAI. To make study comparisons possible, it was an important to determine the presence and activity of GO using standardized scales such as the Clinical Activity Scale (CAS) (Mourits et al. 1989; Mourits et al. 1997) (eye pain, ocular or eyelid erythema, conjunctival or eyelid edema, and worsening of proptosis), and/or NOSPECS (Werner 1969; Werner 1977a,b) (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) that reflected the severity of opthalmopathy. Activity of GO were defined according to the CAS scores of ≤ 3/7. Furthermore, the study has been extended on the basis of consensus of European group on Graves’ orbitopathy (EUGOGO) (Bartalena et al. 2008; www.eugogo.eu). The criteria used during the ophthalmological examination included: visual acuity, cover test, tonometry, colour test, fundus examination, lid fissure measurement, visual field, Hess-Lancaster screen, and Hertel’s exophthalmometer measure. Patients failing to return for follow-up were excluded from the study.

Assessment of smoking history

Urine cotinine level non-smokers: Urine cotinine [(5S)-1-methyl-5-(3-pyridyl)pyrrolidin-2-one], is a nicotine metabolite and therefore a useful reporter of nicotine traces in the human body. Non-smokers and those not exposed to environmental tobacco smoke (ETS) had urine cotinine levels of 5 ng/mL in urine/mg creatinine; individuals exposed to ETS had 5 to 50 ng cotinine in urine/mg creatinine (passive exposure); and smokers >50 ng cotinine in urine/mg creatinine (from 50 to 500 ng/mL in light smokers; 500–2500 ng/mL in moderate smokers, and above 2500 ng/mL in heavy smokers) (Florék et al. 2006).

Chemicals: Cotinine was dissolved in methanol to create a standardized solution in methanol (Wao Pure Chemicals; Osaka, Japan and Sigma Chemical St Louis, MO, USA). The standard solution was added to urine (non-smokers) 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.

Equipment: A gas chromatograph (GC-14B, Kyoto, Japan) equipped with a capillary column and flame thermionic sensor was utilized for quantifying cotinine. The injection port and detector temperature was 260 °C. The column temperature was constant at 150 °C for 2 min, then raised to 260 °C at the rate of 10 °C/min, and held constant for 2 min. as the final temperature. Nitrogen at 15 kPa was the carrier gas.

Measurement: One milliliter of urine was added to 0.1 ml of 12 μg/ml of carbinoxamine maleate in methanol and 1ml 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 s. 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 s. 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. 1 μl of the remaining alcohol solution was then injected into the gas chromatograph.

**Statistical analysis**

All alterations in clinical and biochemical parameters between smokers and non-smokers were carefully evaluated, in particular to urine cotinine concentration reference. Statistical analysis was performed using Statistica 7.1, StatSoft Inc. All the data are presented as mean±(±SEM) unless stated otherwise. The Mann–Whitney U test was applied in a non-parametric distribution. The statistical correlations were assessed by a calculation of Spearman’s coefficient, according to the data distribution. Two-tailed p-values <0.05 were considered statistically significant.

**RESULTS**

The clinical and biochemical characteristics of all the patients studied at baseline and one-year of follow-up after RIT are shown in Table 1 and 2.

**Thyroid function and serology**

The levels of free T4, and free T3 remained stable in both groups throughout one year observation. Serum values of TSH in both groups were undetectable. In smokers, the mean (±S.E.M) serum fT4 levels before RIT were: 22.2±3.7 pmol/l, 22.5±5.1 pmol/l (for 2 months), 19.5±4.2 U/L pmol/l (6 months) and 18.6±6.1 pmol/l (1 year). In non-smokers, serum fT4 levels at time of RIT were: 22.9±4.1, 21.3±4.9 (for 2 months), 18.8±4.1 (6 months) and 17.2±4.3 pmol/l (1 year). The values of the mean (±S.E.M) serum fT3 levels in non-smokers before RAI were: 6.1±2.6 U/L, 4.7±1.2 after 2 months, 5.1±0.3 (6 months), and 3.7±0.7 pmol/l (1 year). In smokers serum fT3 levels at the time of the RIT administration were: 11.1±4.3, 5.8±0.2 (2 months), 5.3±1.4 (6 months), and 5.0±0.8 pmol/l (1 year), respectively. The observed differences were not statistically significant.

At baseline, after 2, 6 and 12 months after RAI the changes in following groups in levels of Tg-Abs were not significant. In smokers the results were: 197.5±121.6 at baseline, 222.5±159.7 after 2 months, 199.4±124.3 (6 months), and 187.2±138.4 IU/ml (1 year) and in non-smokers: 134.1±123.3 at baseline, 243.4±161.6 (2 months), 238.4±221.6 (6 months) and 196.4±154.6 IU/ml (1 year), respectively.

In smokers, the values of serum TPO-Abs were: 284.3±274.8 at baseline, 342.4±293.4 after 2 months, 273.4±194.3 (6 months), and 200.7±214.8 IU/ml (1 year). Statistical significant changes were found for values in the second and sixth month (p<0.05) and in the second and after one year (p<0.005). In non smokers the results were stable and insignificant: 386.2±343.8 at baseline, 343.3±297.4 (6 months), and 214.3±239.7 IU/ml (1 year). The TSHR-Abs concentration was significantly higher in smokers (p<0.05), rising from 22.9±1.2 IU/L before therapy to 29.6±5.3 IU/L – 2 months, 32.6±8.6 IU/L – 6 months, and slightly decreased

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**Tab. 1. Clinical and biochemical characteristics of patients included in the study.**

<table>
<thead>
<tr>
<th>Clinical parameters</th>
<th>Smoking (n=26)</th>
<th>Non-smoking (n=25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F/M</td>
<td>3/23</td>
<td>4/21</td>
</tr>
<tr>
<td>Median age, range (yr)</td>
<td>38 (28–61)</td>
<td>33 (21–54)</td>
</tr>
<tr>
<td>Age at diagnosis (yr)</td>
<td>37±16</td>
<td>36±14</td>
</tr>
<tr>
<td>Duration of GO (months)</td>
<td>8±0.5</td>
<td>11±1.7</td>
</tr>
<tr>
<td>Recent thyroid status (thyroid treatment)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ATD before 131I</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes (%)</td>
<td>25 (96)</td>
<td>25 (100)</td>
</tr>
<tr>
<td>No (%)</td>
<td>1 (4)</td>
<td>-</td>
</tr>
<tr>
<td>Duration ATDs (months)</td>
<td>11.6±15.8</td>
<td>9.8±7.7</td>
</tr>
<tr>
<td>131I</td>
<td>3 (11.5)</td>
<td>-</td>
</tr>
<tr>
<td>Thyroidectomy</td>
<td>-</td>
<td>2 (8)</td>
</tr>
<tr>
<td>Thyroid tests</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TSH (N: 0.27–4.2 µU/mL)</td>
<td>0.07±0.03</td>
<td>0.11±0.05</td>
</tr>
<tr>
<td>FT3 (N: 3.9–6.8 pmol/L)</td>
<td>11.1±4.3</td>
<td>6.1±2.6</td>
</tr>
<tr>
<td>FT4 (N: 11.5–21.5 pmol/L)</td>
<td>22.2±3.7</td>
<td>22.9±3.1</td>
</tr>
<tr>
<td>TSHR-Abs (N: &lt;2 IU/L)</td>
<td>22.9±1.2</td>
<td>15.3±0.2</td>
</tr>
<tr>
<td>Tg-Abs (N: 10–115 IU/ml)</td>
<td>197.5±121.6</td>
<td>134.1±123.3</td>
</tr>
<tr>
<td>TPO-Abs (N: &lt;34 IU/ml)</td>
<td>284.3±274.8</td>
<td>386.2±343.8</td>
</tr>
<tr>
<td>Thyroid volume (ml)</td>
<td>21.3±4.2</td>
<td>16.2±3.1</td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never smoked (%)</td>
<td>-</td>
<td>19 (76)</td>
</tr>
<tr>
<td>Ex-smoker (%)</td>
<td>-</td>
<td>2 (8)</td>
</tr>
<tr>
<td>Current smoker (%)</td>
<td>26 (100)</td>
<td>-</td>
</tr>
<tr>
<td>Passive smoker (%)</td>
<td>-</td>
<td>4 (16)</td>
</tr>
<tr>
<td>Urinary cotinine (ng/mL)</td>
<td>903.4±770.0</td>
<td>5.2±1.7</td>
</tr>
</tbody>
</table>

| Radioiodine treatment                |                |                    |

*ablative dose* of 131I (22.0±0.0 mCi) [814.0±0.0 MBq]  

1,2- Statistical significant differences are related to dependencies between data labeled with the same Arabic numerals. 1 p<0.05, 2p<0.001 (Mann-Whitney test). Numerical variables other than age are given as mean±SD or number (%); M, Male; F, female.

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**Tab. 2. The clinical and biochemical evaluation of patients at different time after radiiodine therapy (RIT).**

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sight loss (Optic Neuropathy) was not taken into con-
sideration because clinical symptoms were mild.

At baseline most frequently observed changes at
baseline in smokers were: eyelid redness (100%), pain
on attempted up or down gaze (61.5%), redness of the
conjunctiva (57.6%) and spontaneous retrobulbar pain
(53.8%). Nevertheless assessing the percentage change
in one-year of clinical follow-up we noted no signifi-
cant alteration for levels of swelling of the eyelids (50% vs
53.8%) and conjunctival edema (50% vs 53.8%).

Although, a rising values were reported for redness of
the conjunctiva (57.6% vs 96.1%), spontaneous retro-
bulbar pain (53.8% vs 76.9%), and inflammation of the
plica (53.8% vs 69.2%). Only in smokers the corneal
involvement and extraocular muscle changes dysfunc-
tion, were observed.

In contradiction, the percentages of occurrence
before RIT OS in non-smokers ranged from 12% (dip-
lopia intermittent) to 84% (eyelid redness) and after
treatment were significantly reduced from 16 % (red-
ness of the conjunctiva) to 48% (pain on attempted
up or down gaze). In one year follow up changes were
positively observed for symptoms such as: redness of
the conjunctiva (48% vs 16%), eyelid redness (84% vs
28%) or pain on attempted up- or down gaze (72% vs
48%). Similarly values remained low for: diplopia
interrupted (12% vs 12%), inflammation of the plica
(36% vs 32%), swelling of the eyelids (32% vs 28%) and
conjunctival oedema (32% vs 28%). Although propto-
sis was stable in both groups, there were no significant
changes noted between smokers and non-smokers in
the observed OS.

DISCUSSION

RIT is the treatment of choice in treating hyperthyroid
patients with Graves’ disease. The usage of this method
in patients with ophthalmopathy, in particular cigarette
smokers, is a controversial therapy due to the elevated
risk of intensifying exophthalmos.
12 months of follow-up.

<table>
<thead>
<tr>
<th>Ophthalmological signs</th>
<th>Before RIT</th>
<th>1/2 year after RIT</th>
<th>1 year after RIT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Smoking</td>
<td>Non-smoking</td>
<td>Smoking</td>
</tr>
<tr>
<td>Spontaneous retrobulbar pain</td>
<td>14 (53.8)</td>
<td>11 (44)</td>
<td>21 (80.7)</td>
</tr>
<tr>
<td>Pain on attempted up- or down gaze</td>
<td>16 (61.5)</td>
<td>18 (72)</td>
<td>15 (57.6)</td>
</tr>
<tr>
<td>Swelling of the eyelids</td>
<td>13 (50)</td>
<td>8 (32)</td>
<td>14 (53.8)</td>
</tr>
<tr>
<td>Eyelid redness</td>
<td>26 (100)</td>
<td>21 (84)</td>
<td>24 (92.3)</td>
</tr>
<tr>
<td>Redness of the conjunctiva</td>
<td>15 (57.6)</td>
<td>12 (48)</td>
<td>13 (50)</td>
</tr>
<tr>
<td>Conjunctivial oedema</td>
<td>13 (50)</td>
<td>8 (32)</td>
<td>14 (53.8)</td>
</tr>
<tr>
<td>Inflammation of the caruncle and/or plica</td>
<td>14 (53.8)</td>
<td>9 (36)</td>
<td>16 (61.5)</td>
</tr>
<tr>
<td>Proptosis *</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RE</td>
<td>17.4±2.9</td>
<td>16.2±2.1</td>
<td>18.4±3.4</td>
</tr>
<tr>
<td>LE</td>
<td>17.2±2.6</td>
<td>16.1±2.2</td>
<td>18.1±2.9</td>
</tr>
<tr>
<td>Diplopia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Absent</td>
<td>21 (80.7)</td>
<td>22 (88.0)</td>
<td>13 (50)</td>
</tr>
<tr>
<td>- Intermittent (morning fatigue)</td>
<td>4 (15.4)</td>
<td>3 (12)</td>
<td>11 (42.3)</td>
</tr>
<tr>
<td>- Constant</td>
<td>1 (3.8)</td>
<td></td>
<td>2 (7.6)</td>
</tr>
<tr>
<td>Extraocular muscle involvement</td>
<td>2 (7.6)</td>
<td>-</td>
<td>2 (7.6)</td>
</tr>
<tr>
<td>Corneal involvement</td>
<td>-</td>
<td></td>
<td>2 (7.6)</td>
</tr>
<tr>
<td>Sight loss (Optic Neuropathy)</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Evidence of OS in NOSPECS scale</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- mild</td>
<td>26 (100)</td>
<td>25 (100)</td>
<td>19 (73)</td>
</tr>
<tr>
<td>- moderate</td>
<td>-</td>
<td>-</td>
<td>7 (27)</td>
</tr>
<tr>
<td>- severe</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>CAS</td>
<td>2.8±0.21</td>
<td>1.4±0.2</td>
<td>4.3±0.3</td>
</tr>
</tbody>
</table>

1,2. Statistical significant differences are related to dependencies between data labeled with the same Arabic numerals. 1p<0.05, 2p<0.005, (Mann-Whitney test). Numerical variables are given as number (%). *Proptosis data are in millimeters. Only CAS and proptosis are shown as mean±SD.

Abbreviations: 1) Absent (NOSPECS 0); 2) Mild (NOSPECS 1: lid lag/retraction); 3) Moderate (NOSPECS 2–3: periocular edema/proptosis); or 4) Severe (NOSPECS 4–6: eye muscle involvement/corneal involvement/sight loss). We elected to categorize the severity of eye disease according to these criteria because this study was performed throughout a time period of 1 yr and NOSPECS scores were documented in all patients; CAS—Clinical Activity Scale: eye pain, ocular or eyelid erythema, conjunctival or eyelid edema, and worsening of proptosis.

It is estimated that approximately 20% of patients develop clinical GO after RIT (Acharya et al. 2008), but those findings are not well documented due to variations in classifying cases as clinical (Marcocci et al. 1999; Rasmussen et al. 2000). According to Vannuchi (Vannuchi et al. 2009), there is no “predictive model” to categorize patients that may be at a higher risk of developing initial or relapsing GO. Currently considered risk factors used to predict GO include: cigarette smoking (associations between GO and ETS) (Bartalena et al. 2002; Bartalena et al. 1998b, Hagg et al. 1987; Hagedus et al. 2004; Kendler et al. 1993; O’Hare & Georghegan 1993; Tomer & Davies 2003; Utiger 1998; Vestergaard 2002; Wiersinga & Bartalena 2002; Winsa et al. 1993; Prummel et al. 2004; Prummel & Wiersinga 1993; Bartalena 2001), high serum TSHR-Ab concentration (Rasmussen et al. 2000; Laurberg et al. 2008), presence of GO at the time of RAI (Laurberg et al. 2008), and fT3 concentration at time of treatment initiation (Sisson et al. 2008).

Concerning our report a recent study published by Vannuchi (Vannuchi et al. 2009) revealed other existing risk factors for the development of GO: the duration of Graves’ disease (>26 months) and recency of GO development (<18 months), being most significant, and to a lesser extent: age (>52 years) and gender (male).

It is considered that the intensification of GO is initiated by 131I promoted autoantigen interacting with orbital tissues, with a longer course from initial clinical diagnosis of Graves’ disease, that is leading to lower autoantigen release after RAI. With duration from diagnosis the infiltration of lymphocytes in both the orbits and thyroid is milder (Armengol et al. 2001; Aust et al. 2004; Ho et al. 2007; Weetman et al. 1989). An increased risk of developing GO after RAI was noted in patients with active or reactivated hyperthyroidism (Salvi et al. 2009; Prummel & Wiersinga 1993; Prummel et al. 1990b), while at the same time an increased TSHR-Ab concentration was associated with GO activity, rising...
even after RIT (Eckstein et al. 2006; Laurberg et al. 2008).

Bartalena (Bartalena et al. 2002, Bartalena et al. 1998; 1998a) was the first who reported that oGCs offered a prophylaxis against GO before and after 131I therapy. In our opinion, the high dose 131I therapy [814 mBq [22 mCi], followed by a complementary therapy with oGCs, is an effective treatment for non-smoking patients (level of urine cotinine was 1.0±1.2 ng/mL) with Graves' hyperthyroidism and does not increase the exponenthalamos.

Although the expression “ablative dose” is often used in the literature instead of high dose, in our opinion it should be kept exclusively for thyroid cancer treatment.

The present study concurs with other results in that smoking clearly increases GO, especially after RIT, even with prophylactic of oGCs. Our work is important because nobody until now described the association of cotinine with ophthalmopathy in such a broad sense. The current study is the first to include urinary cotinine in retrospective studies of cigarette smokers and non-smokers in Graves’ sufferers with mild ophthalmopathy treated with RIT. The urine cotinine concentration is the “gold standard” to measure total nicotine exposure regardless of direct cigarette smoking or environmental exposure (ETS) (Langone et al. 1988). The urine cotinine test is very sensitive and manifested by the fact that even non-cigarette smokers showed this marker of ETS. Hence, the presence of urinary cotinine from cigarette exposure, imply even non-smokers at an increased risk of GO. The accepted standard biochemical test for nicotine absorption is urine cotinine concentration which is specific to cigarette smoke and has half life of 20 hours (Florek et al. 2006). The measure of cotinine in body fluids, regardless of its usefulness, has its limits due to the costs involved and requirements for specialized laboratory equipment (Mascola et al. 1998).

Additionally, the study is presenting the intensity of eye changes associated with RIT-treated patients, in regard of nicotine exposure (Table 3). In particular, the CAS scale is illustrated with the observed intensification of eyelid edema and worsening of proptosis, in smokers even though these changes were not statistically significant, that is proving the benefit of the oGCs prophylaxis. Unfortunately, TSHR-Ab concentration was significantly higher in the smoking group at the beginning and end of our observations. The changes were statistically significant for both groups, which clearly demonstrate that RIT intensifies ophthalmopathy in smokers.

In conclusion: 1) ablative RIT dose with prophylactic oral prednisone is a safe treatment in both smokers and non-smokers with mild GO; 2) The post hoc analysis showed that urinary level of cotinine can be very helpful in the assessment of exacerbation of ophthalmological clinical symptoms before and after RIT particularly in smokers.

REFERENCES


