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Research Article

Graves' Disease in Men's Subjects

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Abstract

Introduction

Graves' disease remains the most frequent cause of hyperthyroidism but poorly described in men. The objective was to study the specificities of Graves' disease in this population at Abass Ndao University Hospital Center in Dakar (Senegal).

Patients and methods

It was a descriptive and analytical retrospective study conducted over 20 years. The parameters taken into account were epidemiological, clinical, and progressive.

Results

624 cases were reported with a prevalence of 28.79% among 2167 cases of Graves' disease. The mean age was 32.1±13 years, family history and irritating factors were respectively found in (15.4%) and (42.46%). The delay of consultation was 11.79±25 months and there were goiter in 89.90% and Graves' orbitopathy in 72.92%. The goiter was statistically correlated with free T4 > 70 pmol/l [OR=2.85(1.53-5.30), p=0.0002] and Graves' orbitopathy with volume of goiter [OR=2.08(1.42-3.07), p=0.0001]. The average starting treatment dose with of Antithyroid Drug (ATD) was 38.3±1 mg/day of Carbimazol. Only a dose of ATD > 30 pmol/l was significantly correlated with early maintenance therapy (≤ 3 months) [OR=0.078(0.04-0.14), p=0.0000].

Complications were thyrotoxic heart diseases (06.89%), moderate-to-severe or sight-threatening orbitopathy (01.12%). After 30 months, 250 subjects (40.06%) were regularly followed. The remission affected 96 patients (38.4%) of whom 26 subjects relapsed at the end of the follow-up. Among the 154 patients (61.60%) who failed treatment, 48 (31.17%) had a thyroidectomy. Failure to medical treatment was significantly correlated with age <30 years [OR=1.96(1.11-3.47), p=0.009], size of goiter [OR=2.50(1.34-4.64), p=0.002] and initial values of free T4 > 70 pmol/l [OR=1.89(1.04-4.42), p=0.017].

Conclusion

Graves' disease in male subject is characterized by delayed diagnosis, a larger goiter, a high rate of lost sight and relapse. The follow-up needs to take into account the risk factors of failure to improve the choices and therapeutic recourses. Radioiodine treatment remains a necessity.

Keywords: Dakar; Graves' disease; Male; Senegal

Introduction

Hyperthyroidism is the most common endocrinopathy whose major etiology is Graves' disease. Graves' disease is characterized by a thyrotoxicosis syndrome associated with a vascular diffuse goiter, a Graves' orbitopathy and presence of anti-TSH receptor antibodies. It is more common in women with a peak frequency between 40 and 60 years [1,2]. Graves' disease is an autoimmune thyroid disorder with a genetic component and environmental factors predisposing to its occurrence. Associated environmental factors include stress, infection and peripartum [3,4]. The pathophysiology of Graves' disease is based on an auto-stimulatory by TSH-Receptor Antibodies (TRAb) on the thyroid gland (vascular goiter), retro-orbital smooth muscle and retro-bulbar fibroblasts (Graves' orbitopathy), and subcutaneous tissue (dermopathy) [5]. The diagnosis associates a thyrotoxicosis and specific signs such as Graves' orbitopathy, vascular goiter and pretibial myxoedema in rare cases. The medical treatment is mainly based on Antithyroid Drug (ATD) treatment over a period of 18 to 24 months. Ablative treatments (i.e., radioiodine therapy and surgery) are the cornerstones of healing. Although the particularities in women are sufficiently well documented [3], specific data in male subjects remain rare, most often embedded in an overall description of Graves' disease. A moroccan series reports on 6 years of follow-up, a mean age of 45 years, a more severe Graves' orbitopathy and a higher relapse rate compared to the female sex [6]. The objective of this work was to study the epidemiological, clinical and evolutionary characteristics of Graves' disease in male subjects at the Medical Clinic II of Abass Ndao University Hospital Center in Dakar (Senegal).

Patients and Methods

This was a descriptive and analytical retrospective study conducted from January 1, 1998 to December 31, 2017 (20 years). It was performed at the Medical Clinic II of Abass Ndao Hospital Center in Dakar (Senegal). The Medical Clinic II houses a hospitalization service of internal medicine with a diabetology orientation, a unit for

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consultation and follow-up of pathologies of internal medicine and endocrinology (including thyroid diseases), diagnostic assistance units and the National Diabetes Center Marc Sankale. We have included the records of male patients with Graves' disease confirmed and followed in the service. Graves' disease is characterized by a thyrotoxicosis syndrome associated with a vascular diffuse goiter or a Graves' orbitopathy. The dosage of the anti-TSH receptor antibodies is not always available on the Senegal. Incomplete or misinformed files were excluded.

The parameters considered in the evaluation were:

Epidemiological aspects

Age divided into children (under 11 years), adolescents (from 11 to 20 years old), adults (over 20 years old), family history of thyropathy, and trigger or self-maintenance factors (family difficulties, professional, and other difficulties).

Clinical aspects

Delay of consultation, anthropometric data. The existence of a Graves' orbitopathy [7], a goiter (classed in grade according to the World Health Organization classification) [8], the values of free Tetra iodothyronine (free T4), free Triiodothyronine (T3 free) and ultrasensitive Thyroid Stimulating Hormone (TSHus) were also evaluated at baseline and at follow-up. The biochemical standards in our laboratory were 0.17 to 4.05 mIU/l for TSHus, 9 to 22 pmol/l for free T4 and 2.5 to 5.8 pmol/l for free T3. Cervical ultrasound with doppler was systematic in case with goiter. Scintigraphy and assay of anti-TSH receptor antibodies were not regularly performed because few available in Senegal.

Treatment and evolution

The modalities of medical and surgical management (no patient had benefited radioiodine therapy unavailable in Senegal) were evaluated over a period of 30 months. We studied the prescribed drugs (antithyroid drug, beta-blockers and anxiolytics), drug dosages at the beginning and during the follow-up. Carbimazol was the only one antithyroid drug used in the medical treatment of Graves' disease. The efficiency of the treatment was based on an overall assessment (clinical, changes in Carbimazol doses and biological parameters, appearance of complications). The remission was a stabilization of the disease after 12 months of discontinuation of medical treatment. Relapse was defined as a reappearance of thyrotoxicosis after a successful cessation of medical treatment. Failure of medical treatment was defined by a poor recovery of the disease occurring during treatment [9,10]. The latter also concerned the voluntary cessation of treatment for whatever reason and loss of sight. Complications sought were thyrotoxic heart diseases [11], acute thyrotoxic crisis, moderate-to-severe or sight-threatening orbitopathy [7], and agranulocytosis. The care of the complications is multidisciplinary with the cardiologists in case of thyrotoxic heart diseases and the ophthalmologists in case of moderate-to-severe or sight-threatening orbitopathy. Indications for thyroidectomy were also taken into account.

For the descriptive analysis, the data were presented as a percentage for the qualitative variables and as averages with standard deviation for the quantitative variables. The statistical tests used were the Chi-2 test for qualitative variables and the student's test for quantitative variables. We also made a univariate analyze to evaluate the factors associated with relapse. A p value < 0.05 was considered statistically significant with a 95% Confidence Interval (CI). The capture and the exploitation were carried out by the software Epi info version 7.2.2.2.

Results

Epidemiological and clinical data

A total of 624 cases of Graves' disease were collected in male subject. The prevalence was 6.4% among 9750 cases of all thyropathies, 24.60% among 2536 cases of hyperthyroidism and 28.79% among 2167 cases of Graves' disease. The average age was 32.1±13 years. A family history of thyroid disease was found in 97 patients (15.4%) and a trigger or self- maintenance factors in 265 subjects (42.46%).

The average delay of consultation was 11.79±25 months (range 1 to 36 months). The mean heart rate was 104 pulses/mn and tachycardia was found in 308 patients (50.08%). It was a goiter in 561 cases (89.90%), a Graves' orbitopathy in 455 cases (72.92%). All patients had a TSH <0.01 mIU/ml. Free T4 value was normal in 139 cases (22.27%), between 23 and 49 pmol/l in 175 cases (28.04%), between 50 and 100 pmol/l in 50 cases (8.01%) and greater than 100 pmol/l in 260 patients (41.66%). The presence of goiter was statistically correlated with the value of free T4 > 70 pmol/l [OR=2.85(1.53-5.30) p=0.0002]. Graves' orbitopathy was statistically correlated with the size of goiter [OR=2.08(1.42-3.07) p=0.0001]. We found no significant correlation with family history thyropathy, trigger or self-maintenance factors, delay of consultation, and age. Table 1 shows the epidemiological and clinical profile of subjects on admission.

Characteristics of patients on admission	Values
Sociodemographic data	
Mean age	32.1±13 years
Children	28 cases (04.49%)
Teenager	82 cases (13.40%)
Adults	514 cases (82.37%)
Triggers or self maintaining factor	265 cases (42.46%)
Abandonment or isolation	67 cases (10.74%)
Family conflict	65 cases (10.42%)
Professional difficulties	137 cases (21.10%)
Clinical and para clinical data	
Delay of consultation	11.79±25 months
Thinness	321 cases (51.44%)
Overweight and obesity	22 cases (03.52%)
Mean heart rate	104±16 pulses/mn
Graves' orbitopathy	455 cases (72.92%)
Goiter	561 cases (89.90%)
Goiter grade 2	212 cases (33.97%)
Goiter grade 3	254 cases (40.71%)
Goitre and Graves' orbitopathy	415 cases (66.5%)
Mean free T4	71.8±51 pmol/l

Table 1: Epidemiological and clinical profile of subjects at admission.

Therapeutic data

All patients had initially received medical treatment with ATD (only Carbimazol). The average starting dose of treatment was 38.3±1

mg/day. This dose was less than 30 mg/day in 35.97% of cases, between 30 and 50 mg/day in 53.71%. In 10.32% of cases, it was greater than 50 mg/day. Anxiolytics and beta blocker was prescribed in 244 patients (39.10%) and 350 patients (56.09%), respectively. The simultaneous use of beta blockers and anxiolytics was found in 227 patients (36.37%). The mean duration of the attack treatment was 6.73 months. Among the patients who complied with their appointment, the maintenance treatment was effective in the first 3 months in 282 (61.84%), within 6 months in 310 patients (79.69%). Only the ATD peak dose > 30 pmol/l was significantly correlated with early initiating maintenance treatment in the first 3 months [OR=0.078(0.044-0.14) p=0.0000]. We don't found a significant correlation between early initiating maintenance treatment and respectively the initial free T4 value, the use of beta blocking or anxiolytics therapy.

Evolutive data

Among the 624 patients initially selected, those lost to follow-up represented 229 cases (36.69%) at 6 months and 334 cases (53.52%) at 12 months of follow-up. Complications were thyrotoxic heart diseases in 43 cases (06.89%), moderate-to-severe or sight-threatening orbitopathy in 7 cases (01.12%), and agranulocytosis in 2 cases. We did not find an acute thyrotoxic crisis.

After 30 months, only 250 subjects were regularly followed, with a percentage of 40.06%. Remission was observed in 96 patients (38.40%). Among them, 26 subjects (27.03%) had relapse. The 70 patients (28%) with full remission had a remission delay of 15 months in 45 cases (64.29%), 18 months for 14 cases (20%), and 21 months in 10 cases (14.29%). A failure of medical treatment was found in 154 patients (61.60%). Among the subjects with treatment failure, 48 (31.17%) had a thyroidectomy; the others (68.83%) are still under ATD treatment. Indications for thyroidectomy were failure of medical treatment in 33 cases, thyrotoxic heart diseases in 11 cases (23.40%), moderate-to-severe or sight-threatening orbitopathy in 2 cases (04.25%) and agranulocytosis in 2 cases.

Failure to medical treatment was significantly correlated with age < 30 years [OR=1.96(1.11-3.47), p=0.009], presence of goiter [OR=3.43(1.41-8.37), grades of goiter [OR=2.50(1.34- 4.64), p=0.002] and initial values of free T4 > 70 pmol [OR=1.89(1.04-4.22), p=0.017]. Other parameters such as body mass index, family history of thyropathy, trigger or self-maintenance factors, delay of consultation, Graves' orbitopathy, and Carbimazol initial dose were not shown to be significant. Table 2 shows the factors associated with the failure of medical treatment in the 250 male subjects who completed 30 months of treatment.

Evolutionary criteria (n=250 subjects)	Therapeutic failure		Odds ratio (95% IC), p value
	Yes (n=180)	No (n=70)	
Age < 30 years	94 (52.22%)	25 (35.71%)	1.96 (1.11-3.47), p=0.009*
Body mass index < 25 kg/m²	145 (96.03%)	47 (94%)	1.54 (0.37-6.41), p=0.277
Delay of consultation < 12 mois	125 (70.22%)	45 (67.16%)	1.15 (0.63-2.10), p=0.321
Triggers or self maintaining factor	95 (52.78%)	30 (42.86%)	1.94 (0.85-2.59), p=0.081
Family thyropathy	36 (20.00%)	10 (14.28%)	1.53 (0.72-3.29), p=0.136
Goiter	169 (93.88%)	59 (83.10%)	3.43 (1.41-8.37), p=0.003*
Goiter grades 2 et 3	147 (81.66%)	46 (65.71%)	2.50 (1.34-4.64), p=0.002*
Graves' orbitopathy	138 (76.66%)	51 (72.85%)	1.32 (0.71-2.46), p=0.193
Free T4 value > 70 pmol/l	77 (44.77%)	21 (30%)	1.89 (1.04-3.42), p=0.017*
Initial Carbimazol dose < 40 mg/24h	126 (70%)	48 (68.57%)	1.06 (0.58-1.94), p=0.410

Table 2: Factors associated with failure of medical treatment in the 250 subjects followed for 30 months.

Discussion

Epidemiological and clinical data

Epidemiological data on Graves' disease in male subjects remain variously reported by series and authors. In the western countries, frequencies vary from 12.1% in French [9] to 17.2% in the United Kingdom [12]. In Africa, values between 8.6% and 12.4% are found [13,14]. Like data in our patients, the average age stabilizes between 35 and 45 years [13,14,15-18]. The inclusion of children and adolescents partly explains the decline of this average age to 32.1 years in our study.

The importance of the environment and genetics in the genesis of Graves' disease is well known [19-21]. These include smoking, triggers or self maintaining factors, and a family history of thyroid disease [12,18,22]. In male subjects, Manji et al. [18], and Allahabadia et al. [12], in the United Kingdom respectively reported a family history of thyropathy in (40% and 42.5%) and active smoking in (31.4% and 44%). For Magri et al. [23], in Italy, the existence of family thyropathy was significantly more common in men. The profile of maintenance factors for the disease would rather depend on societal realities. Diop et al. [24], had already described the role and impact of stress in the onset of Graves' disease. In Senegal, Sarr et al. [13], found family conflict and psycho-emotional shock in 22.8% and 14.9% respectively.

The frequency of the specific signs of Graves' disease was almost identical to the literature data [10,13 14,25,26]. The presence of goiter seems less frequent compared to the female sex [12,18]. But male subjects would be characterized by a larger goiter [18,23]. As previously described in the literature, the presence of goiter in the male subject was statistically correlated with young age, Graves' orbitopathy, and free T4 value [12,18,19,23].

Therapeutic aspects

For medical treatment, the recommendations suggest an adaptation of the initial dose of ATD to the intensity of hyperthyroidism and profile of the patient [10]. This is to obtain at the same time anti-thyroid and immunosuppressive actions without major adverse effects [27-29]. Our study also shows a significant correlation between the intensity of the initial dose of ATD and the early maintenance treatment. The β blockers play a major role in controlling the symptoms of thyrotoxicosis. Aside from their inhibitory action on cardiovascular symptoms, they would block the peripheral transformation of Tetraiodothyronine (T4) into the more active Triiodothyronine (T3).

Their prescription should be systematic until euthyroidism. To this prescription, should be added a supportive psychotherapy and anxiolytics. As in our study, the first-line medical treatment remains the preference in Europe, Latin America and Japan; in contrast to the USA where it is rather radioiodine therapy with Iodine 131 which predominates in 59.7% [10].

If the patient remains in persistent hyperthyroidism beyond 2 years of medical treatment, the surgical indication should be considered. However, the option of prolonged low-dose medical treatment may be used in case of patient preference [10,30]. In the absence of radioiodine therapy not available in Senegal, many of our patients preferred the long-term medical option despite its inefficiency.

Evolutionary data

In Sub-Saharan Africa, spontaneous therapeutic disruption is the main obstacle to optimizing treatment [20]. In addition to the delay in management, this fact explains the high rate of mainly cardiovascular complications. They were reported at 9.8% and 16.6% respectively in Senegal [31] and Morocco [6]. However, it is rather the female sex which would be more at risk of thyrotoxic heart diseases [31].

The frequency of remission varies considerably by geographical area. After 30 months of follow-up, we report a complete remission in 28%. In the USA, remissions in 20 to 30% were reported after 12 to 18 months of medication [32]. A European study of 5 to 6 years of medical treatment reports a remission in 50 to 60% [33]. However, the remission rate in adults would not be improved by medical treatment beyond 18 months [34] or high doses of initial treatment by ATD [35]. In addition, the male sex is more likely to recur, especially in smokers and those with large goiter [6,12,36,37]. In our study, failure in medical treatment was significantly correlated with young age [OR=1.96(1.11-3.47), p=0.009], goiter size [OR=2.50(1.34-4.64), p=0.002] and intensity of hyperthyroidism [OR=1.89(1.04-4.42), p=0.017].

Conclusion

Graves' disease in male subjects remains an underrated reality. It is characterized by a delay in diagnosis, a larger goiter, a high rate of lost sight and more relapse. Apart from therapeutic education, patient support remains essential. The follow-up will have to take into account the risk factors of failure to improve the choices and therapeutic recourses. The fear of thyroidectomy should lead us to more advocacies to make available radioiodine therapy.

Conflict of Interest

The authors do not declare any conflict of interest.

References

1. Girgis CM, Champion BL, Wall JR (2011) Current concepts in Graves' disease. Ther Adv Endocrinol Metab 2: 135-144.
2. Franklyn JA, Boelaert K (2012) Thyrotoxicosis. The Lancet 379: 1155-1166.
3. Phillipe JM (2009) Graves's disease in 2009. Rev Med Suisse 5: 764-768.
4. Brent GA (2008) Clinical practice Graves disease. N Engl J Med 358: 2594-2605.
5. Orgiazzi J (2013) Thyroid autoimmunity. Bull Acad Natle Méd 197: 43-63.
6. Bouziane T, Larwanou M, El Ouahabi H (2017) The predictive factors of relapse in Graves disease treated by ATS: About 72 cases. Ann Endocrinol 78: 326-352.
7. Bartalena L, Baldeschi L, Dickinson AJ, Eckstein A, Kendall-Taylor P, Marcocci C, et al. (2008) Consensus statement of the European Group on Graves' Orbitopathy (EUGOGO) on management of GO. Eur J Endocrinol 158: 273-285.
8. World Health Organization (1994) United nation children's fun & international council for control of iodine deficiency disorders Indicators for assessing iodine deficiency disorders and the control through salt iodization. World Health Organization, Geneva, Switzerland. Pg no: 1-55.
9. Goichot B, Caron P, Landron F, Bouée S (2016) Clinical presentation of hyperthyroidism in a large representative sample of outpatients in France: Relationships with age, etiology and hormonal parameters. Clin Endocrinol (Oxf) 84: 445-445.
10. Ross DS, Burch HB, Cooper DS, Greenlee MC, Laurberg P, et al. (2016) 2016 American thyroid association guidelines for diagnosis and management of hyperthyroidism and other causes of thyrotoxicosis. Thyroid 26: 1343-1421.
11. Dahl P, Danzi S, Klein I (2008) Thyrotoxic cardiac disease. Curr Heart Fail Rep 5: 170-176.
12. Allahabadia A, Daykin J, Holder RL, Sheppard MC, Gough SCL, et al. (2000) Age and gender predict the outcome of treatment for Graves' hyperthyroidism. J Clin Endocrinol Metab 85: 1038-1042.
13. Sarr A, Diédhiou D, Ndour-Mbaye NM, Sow D, Diallo IM, et al. (2016) Graves' disease in Senegal: Clinical and evolutionary aspects. Open Journal of Internal Medicine 6: 77-82.
14. Diagne N, Faye A, Ndao AC, Djiba B, Kane BS, et al. (2016) Epidemiological, clinical, therapeutic and evolutive aspects of Basedow-Graves disease in the Depatment of Internal Medicine at CHU Aristide Le Dantec, Dakar (Senegal). Pan Afr Med J 25: 6.
15. Bilosi M, Binquet C, Goudet P, Lalanne-Mistrih ML, Brun JM, et al. (2002) [Is subtotal bilateral thyroidectomy still indicated in patients with Grave's disease?]. Ann Chir 127: 115-120.
16. Hussain YS, Hookham JC, Allahabadia A, Balasubramanian SP (2017) Epidemiology, management and outcomes of Graves' disease - Real life data. Endocrine 56: 568-578.
17. Abodo J, Kélie E, Koffi Dago P, Kouassi F, Hué LA, Lokrou A (2016) Profile of the thyroid pathologies in sub-Saharan Africa: About 503 cases. Ann Endocrinol 77: 372-412.
18. Manji N, Carr-Smith JD, Boelaert K, Allahabadia A, Armitage M, et al. (2006) Influences of age, gender, smoking, and family history on autoimmune thyroid disease phenotype. J Clin Endocrinol Metab 91: 4873-4880.
19. Boiro D, Di**édh**iou D, Niang B, Sow D, Mbodj M, et al. (2017) [Hyperthyroidism in children at the University Hospital in Dakar (Senegal)]. Pan Afr Med J 28: 10.
20. Akossou SY, Napporn A, Goeh-Akuee E, Hillah A, Sokpoh-Diallo K, et al. (2001) [Problems in the management of thyrotoxicosis in Black Africa: The Tongolese experience]. Ann Endocrinol (Paris) 62: 516-520.
21. Léger J, Carel JC (2013) Hyperthyroidism in Childhood: Causes, when and how to treat. J Clin Res Pediatr Endocrinol 5: 50-56.
22. Deleveaux I, Chamoux A, Aumaître O (2013) Stress and auto-immunity. Rev Med Interne 34: 487-492.

23. Magri F, Zerbini F, Gaiti M, Capelli V, Ragni A, et al. (2016) Gender influences the clinical presentation and long-term outcome of Graves disease. Endocr Pract 22: 1336-1342.

24. Diop SN, Diédhiou D, Sarr A, Ndour Mbaye M, Sylla O, et al. (2011) Psychological aspects and psychiatric manifestation of grave's disease about 104 cases. Rev Cames 12: 62-64.

25. Hadj Ali I, Khiari K, Chérif L, Ben Abdallah N, Ben Maiz H, et al. (2004) [Treatment of Graves' disease: 300 cases]. Presse Med 33: 17-21.

26. Morax S, Badelon I (2009) Basedow exophthalmos. J Fr Ophtalmol 32: 589-599.

27. Nakamura H, Noh JY, Itoh K, Fukata S, Miyauchi A, et al. (2007) Comparison of methimazole and propylthiouracil in patients with hyperthyroidism caused by Graves' disease. J Clin Endocrinol Metab 92: 2157-2162.

28. Page SR, Sheard CE, Herbert M, Hopton M, Jeffcoate WJ (1996) A comparison of 20 or 40 mg per day of carbimazole in the initial treatment of hyperthyroidism. Clin Endocrinol (Oxf) 45: 511-516.

29. Wartofsky L, Glinoer D, Solomon B, Nagataki S, Lagasse R, et al. (1991) Differences and similarities in the diagnosis and treatment of Graves' disease in Europe, Japan, and the United States. Thyroid 1: 129-135.

30. Villagelin D, Romaldini JH, Santos RB, Milkos A, Ward LS (2015) Outcomes in relapsed Graves' disease patients following radioiodine or prolonged low dose of methimazole treatment. Thyroid 25: 1282-1290.

31. Diédhiou D, Sow D, Lèye MM, Diallo IM, Bodian M, et al. (2017) Cardiothyreosis: Risk factors and clinical profile. Open Journal of Internal Medicine 7: 1-11.

32. Klein I, Becker DV, Levey GS (1994) Treatment of hyperthyroid disease. Ann Intern Med 121: 281-288.

33. Mazza E, Carlini M, Flecchia D, Blatto A, Zuccarini O, et al. (2008) Long-term follow-up of patients with hyperthyroidism due to Graves' disease treated with methimazole. Comparison of usual treatment schedule with drug discontinuation versus continuous treatment with low methimazole doses: A retrospective study. J Endocrinol Invest 31: 866-872.

34. Abraham P, Avenell A, Park CM, Watson WA, Bevan JS (2005) A systematic review of drug therapy for Graves' hyperthyroidism. Eur J Endocrinol 153: 489-498.

35. Kruljac I, Solter D, Vrkljan AM, Solter M (2015) Remission of Graves' disease is not related to early restoration of euthyroidism with high-dose methimazole therapy. Endocr Res 40: 25-28.

36. Bolanos F, Gonzalez-Ortiz M, Duron H, Sanchez C (2002) Remission of Graves' hyperthyroidism treated with methimazole. Rev Invest Clin 54: 307-310.

37. Kimball LE, Kulinskaya E, Brown B, Johnston C, Farid NR (2002) Does smoking increase relapse rates in Graves' disease? J Endocrinol Invest 25: 152-157.