

Original article

# A questionnaire survey on the management of Graves' orbitopathy in China: A comparison with Europe and Latin-America

Shu-Hang Xu, Xing-Jia Li, Guo-Fang Chen, Quan-Xi Zheng, Yu Yang, Yong-Xin Hu, Kun Wang, Chao Liu\*

*Endocrine and Diabetes Center, Jiangsu Province Hospital on Integration of Chinese and Western Medicine, Nanjing University of Traditional Chinese Medicine, Jiangsu Branch of China Academy of Chinese Medical Science, Nanjing, Jiangsu, 210028, China*

Received 2 December 2014  
Available online 7 July 2015

## Abstract

**Objective:** Management of Graves' orbitopathy (GO) continues to be a challenge to clinical endocrinologists. In the last few years, surveys on GO management have succeeded in elucidating trends in Europe and Latin America. To determine how endocrinologists in China assess and treat patients with GO and gain insight into how to make the management of this disease more uniform and standardized.

**Methods:** Based on the questionnaire used in the European survey on GO, a questionnaire in China was drafted and circulated to the members of Chinese Society of Endocrinology (CSE) during the annual meeting.

**Results:** A total of 124 valid responses were analysed. Almost all respondents (94.4%) claimed that a multidisciplinary approach for GO management was valuable. Over 80% of the participants advocated the assessment of exophthalmometry, vision, visual fields by perimetry, eye movements, and fundoscopy. Glucocorticoids were preferred as the first-line therapy by 92.7% of respondents, among them, 59.7% choose the intravenous route. The treatment strategy for GO with intravenous glucocorticoids therapy still remains debatable. Anti-thyroid drugs (ATDs) were the most common choice (72.6%) for first-line therapy of coexisting hyperthyroidism. Treatment options for GO were very similar among Chinese, Latin-American and European respondents, whereas radioactive iodine and surgical treatment were more often indicated for co-existing hyperthyroidism in China.

\* Corresponding author. 1 Huadian Road, Nanjing, 210028, China. Tel.: +86 13337806688.

E-mail address: [liuchao@nfmcn.com](mailto:liuchao@nfmcn.com) (C. Liu).

Peer review under responsibility of Chinese Medical Association.



**Conclusion:** The appropriate treatment for patients with GO is controversial even among thyroid specialists. Further training of thyroid specialists, easier access of patients to multidisciplinary centres and establishment of practice guidelines are required for the management of this condition in China.

© 2015 Chinese Medical Association. Production and hosting by Elsevier B.V. on behalf of KeAi Communications Co., Ltd. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

*Keywords:* Graves' orbitopathy; Thyrotoxicosis; Questionnaire survey

## Introduction

Graves' orbitopathy (GO), a comorbidity of Graves' disease, remains a challenge for clinical endocrinologists. The prognosis is usually unfavorable and it requires multidisciplinary collaborations of radiologists, ophthalmologists and surgeons. The prevalence of GO is approximately 0.25% in the general population, and about 30–50% of Graves' patients have clinically apparent ophthalmopathy.<sup>1</sup> GO patients are also at high risks of sick leaves, permanent work disability and early retirement. It was reported that direct costs per year were higher in sight-threatening GO than in moderate-to-severe or mild GO.<sup>2</sup> Therefore, early diagnosis and intervention of GO is essential not only from the public health perspective, but also from an economic one.

The most appropriate approach to treat GO is not been identified yet and using glucocorticoids for treating the severe forms of GO remains controversial. The European Group on Graves' Orbitopathy (EUGOGO) and the Latin American Thyroid Society (LATS) conducted questionnaire surveys targeting their members. They found big differences among thyroid experts in treating GO.<sup>3,4</sup> Glucocorticoids were recommended by most respondents, but the ways of using glucocorticoids (orally or intravenously, alone or in combination with other treatments) differ from each other substantially. Moreover, potential problems in the diagnosis and management of GO and coexisting hyperthyroidism were identified in these studies.

The present study aims to investigate the current status of GO evaluation and treatment among Chinese endocrinologists and compare with Latin American and European.

## Materials and methods

Based on the questionnaire used in the European survey on GO, a questionnaire in Chinese was drafted

and circulated among members of Chinese Society of Endocrinology (CSE) during the 11th Annual Meeting of CSE in Guangzhou, China, 2012.

There are two parts and 18 questions in the questionnaire. In the first part, all participants were asked to give their general impressions on GO in their daily practice. The second part is about a description of an index case (Table 1). Questions related to the index case were asked, with the focus on GO diagnosis and treatment; specifically steroids usage and management of co-existing hyperthyroidism (Table 2).

Data were typed into a computer operated database (Microsoft Excel 2010; Microsoft, Atlanta, USA) and analysed using Graphpad Prism5 software (GraphPad Software Inc., San Diego, USA). Results were predominantly given as frequencies, and  $\chi^2$  tests were used to compare among China, Europe and Latin America. A *P* value <0.05 was considered statistically significant.

Table 1

Index case: patient with moderate to severe GO and hyperthyroidism.

### Index case

A 65-year-old female patient presents with typical symptoms of hyperthyroidism. She also gives a 6-week history of uncomfortable watery eyes; lid swelling in the mornings and double vision on upward and lateral gaze. She smokes 15–20 cigarettes per day. On examination, she is found to be moderately thyrotoxic. She has an easily palpable but small symmetrical goitre. There is marked periorbital edema, redness of the conjunctivae, bilateral chemosis and obvious restriction of eye movements on upward gaze, and attempts to look up provoke retro-orbital pain. Proptosis is 19 mm bilaterally. Her visual acuity is normal (6/6–1.0, bilaterally on the Snellen chart). On direct questioning, she admits to being aware that colors appear less bright than they did two weeks earlier. Fundoscopy shows normal optic disks. Biochemistry confirms thyrotoxicosis (free thyroxine 52 pmol/L, normal range 11–23; total tri-iodothyronine 9.3 nmol/L, normal range 1–2.9; thyroid-stimulating hormone (0.05 mU/L).

GO: Graves' orbitopathy.

Table 2  
Percentages of responders who suggested different tests for the index patient with GO ( $n = 124$ ).

	%
Exophthalmometry	98.4
TSH receptor antibodies	96.8
Thyroid function	96.8
Visual acuity	94.4
Visual fields by perimetry	91.9
Eye movement	89.5
Fundoscopy	88.7
Thyroid ultrasonography	87.9
Ophthalmic ultrasonography	74.2
Eye muscle antibodies	73.4
Corneal evaluation	62.9
Measurement of palpebral fissure	53.2
CT scan	53.2
Magnetic resonance imaging	50.8
Plasma plus urinary glycosaminoglycans	46.0
Color vision	42.7
Radiolabelled-octreotide scintigraphy	27.4

GO: Graves' orbitopathy; TSH: thyroid-stimulating hormone.

## Results

### General information

Questionnaires from 149 respondents were retrieved from 300 distributions. Questionnaires with missing information were excluded ( $n = 25$ ), leaving a total of 124 for analysis. The overall response rate was 41.3%, significantly higher than that of surveys conducted in Europe in 2006 (22.8%)<sup>3</sup> and in Latin America in 2008 (33.8%).<sup>4</sup>

There were 11 respondents who met with more than 500 patients with Graves' disease during previous six months of the survey, whereas there were only nine who saw fewer than 10 cases. Overall, two and seven respondents treated at least 100 and 50–99 GO cases, respectively, whereas the majority (92.7%) treated fewer than 50 cases. More than half of the respondents (53.2%) thought the GO prevalence were 'increasing' or 'unchanged'. Almost all respondents (94.4%) claimed that it was highly desirable to treat GO in a multidisciplinary approach, as well as to establish clinical guidelines for the management of the disease.

### Assessment and diagnosis of GO

The index patient was featured in the case report with a history of colour desaturation, but with normal visual acuity (Table 1). The majority of respondents (85.4%) replied that they would treat her in an out-

patient clinic, while only 10.3% replied that the patient should be hospitalized in the Endocrinology Department. The remaining four respondents would have the patient referred to an ophthalmologist.

Tests were listed as possible choices for diagnosis (Table 2). All participants opted to use at least two diagnostic tests. Beside thyroid function, exophthalmometry (98.4%), thyroid-stimulating hormone (TSH) receptor antibodies (96.8%), visual acuity (94.4%), visual fields by perimetry (91.9%), eye movement (89.5%), fundoscopy (88.7%) and thyroid ultrasonography (87.9%) were the most commonly selected tests. About half of the respondents recommended computed tomography scans (CT scans, 53.2%) as well as magnetic resonance imaging (MRI, 50.8%), and only 27.4% preferred radiolabelled-octreotide scintigraphy. Suggestions for further investigation varied among respondents.

### Treatment of GO

As the initial treatment, both general (avoid corneal exposure, wear protective glasses, etc.) (96.8%) and specific approaches (quit smoking) (92.7%) were recommended by the vast majority of respondents. In addition, diuretics were suggested by 48.4%.

The percentages of respondents who selected different therapeutic approaches for moderate or severe GO are shown in Fig. 1. Glucocorticoids were recommended by 92.8% of respondents, either alone or combined with radiotherapy, decompressive surgery,

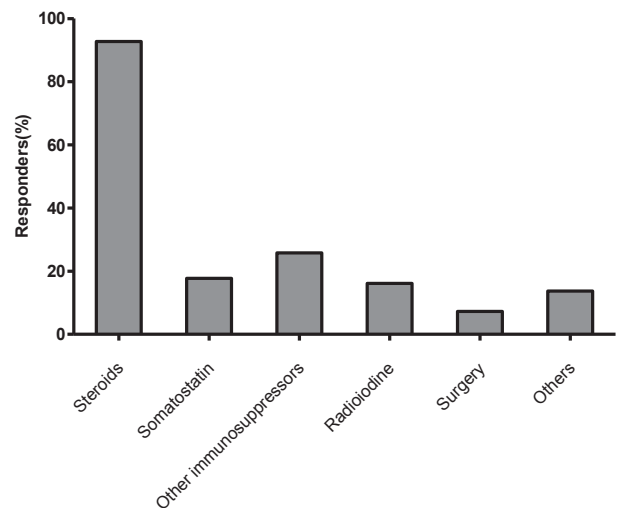


Fig. 1. Initiation treatment choices for index case at index patient's first presentation.

etc. Among them, the majority of participants preferred glucocorticoid therapy alone, while only 18.3% and 10.4% chose combined therapies with somatostatin and other immunosuppressors, respectively. The preferred route of administration for steroids was intravenous (59.7%), followed by oral administration (23%) and a combination of both (13.7%), plus uncertain from four respondents.

For intravenous methylprednisolone treatment, four different therapeutic approaches commonly seen in the literature<sup>5</sup> were provided in this survey<sup>1</sup>: 12-week course, 0.5 g/week intravenous methylprednisolone for six consecutive weeks followed by 0.25 g/week for six weeks<sup>2</sup>; 3-day course, 0.5–1 g/d intravenous methylprednisolone for three consecutive days, followed by tapering dose of oral prednisolone<sup>3</sup>; 8-week course, four cycles 15 mg/kg intravenous methylprednisolone biweekly (bw), then four cycles 7.5 mg/kg intravenous methylprednisolone bw<sup>4</sup>; 6-week course, 0.5–1 g/d intravenous methylprednisolone for 3–5 consecutive days repeated once weekly over five weeks. Among those respondents preferring intravenous glucocorticoid treatment, 50.4%, 37.8% and 16.2% chose the 1st, 2nd and 4th approaches, respectively. Only one respondent opted for the 3rd option, while five had other terms without enough details mentioned.

In light of serious adverse events including Cushing's Syndrome, osteoporosis as well as potential cardiovascular and hepatic risks, the dose and duration of oral and intravenous glucocorticoid treatment should be decided carefully by all endocrinologists. Overall, 32.3% and 49.2% of respondents recommended total durations of glucocorticoid therapy within 1–3 months and 3–6 months, respectively. The dose of glucocorticoids, either initially or during the entire treatment, was also recorded by the respondents. Of those initiating oral glucocorticoids as the first-line therapy ( $n = 29$ ), 18 respondents chose a dose range of 10–30 mg prednisolone (or equivalent), while eight chose >30–60 mg and three chose >60 mg. For intravenous methylprednisolone, 40.3% respondents recommended a cumulative dose of less than 8 g in a single course, while 14.5%, 20.2%, and 5.6% recommended <5 g, <12 g, and <16 g, respectively. Among other immunosuppressive agents to be used in case of unsatisfactory efficacy or severe side effects of glucocorticoid therapy, cyclophosphamide and cyclosporine A were each recommended by 50.8% and 36.3% of respondents, respectively. Others included intravenous immunoglobulins (11.3%), tacrolimus (2.4%), and mycophenolate mofetil (10.5%).

### Treatment of co-existing hyperthyroidism

Anti-thyroid drugs (ATDs) were the most predominant choice (72.6%) as the first-line therapy for co-existing hyperthyroidism in the above case. Radioiodine was chosen only by 16.1%, and surgery by 9.7%. If surgery was being planned, 55.6% would prescribe prophylactic corticosteroids. Of these participants, 63.7% recommended prednisolone 20–40 mg (or equivalent). Half of the respondents replied that thyroid surgeries should be determined by surgeons, whereas 37.1% chose near total thyroidectomy as their initial treatment because recurrence of hyperthyroidism would not be seen. If radioiodine was recommended to the patient in this case, prophylactic glucocorticoids were suggested by the majority (64.7%), whereas they were opposed by 7.3%. The appropriate dose of glucocorticoids remains controversial: 31.5% preferred <30 mg prednisolone (or equivalent), 27.4% preferred 30–100 mg, and 4.8% preferred >100 mg. Other respondents recommended postoperative use of glucocorticoids.

### Compared to the European and Latin-American surveys

Compared to European<sup>3</sup> and Latin-American<sup>4</sup> surveys, choices for the treatment of GO were very similar. There were no significant differences of glucocorticoid use, orbital irradiation, and decompressive surgery between our survey and theirs (Table 3). Orbital irradiation and decompressive surgery in Europe were more often indicated for the case patient than they were in China (23.8% vs. 16.1%,  $P > 0.05$ ) and Latin-America (23.8% vs. 17.0%,  $P > 0.05$ ). By contrast, discrepancies exist in treatment preferences of hyperthyroidism

Table 3

A comparison of treatment options for GO and hyperthyroidism among Chinese, European and Latin-American surveys.

Items	China	Europe	Latin-America
Total number of responders	124	108	102
Treatment for GO			
Steroids (%)	92.7	90.5	88.2
Orbital irradiation (%)	16.1	23.8	17
Surgery (%)	7.3	20.9	7
Treatment for comorbid thyrotoxicosis			
ATDs (%)	72.6	90.9**	86.2*
Radioiodine (%)	16.1	2**	5.9*
Surgery (%)	9.7	3	0**

GO: Graves' orbitopathy; ATDs: antithyroid drugs.

Compared to China, \* $P < 0.05$ , \*\* $P < 0.01$ .

among these three surveys (Table 3). ATDs were less frequently recommended by Chinese respondents than by European (72.6% vs. 90.9%,  $P < 0.01$ ) and Latin-American respondents (72.6% vs. 86.2%,  $P < 0.05$ ). Chinese respondents were more likely to use radioiodine than European (16.1% vs. 2.0%,  $P < 0.01$ ) and Latin-American respondents (16.1% vs. 5.9%,  $P < 0.05$ ), as well as thyroidectomy (9.7% in China vs. 3.0% in Europe,  $P > 0.05$  and 9.7% in China vs. 0% in Latin-America,  $P < 0.01$ ).

## Discussion

GO is an autoimmune process and very common extra-thyroidal manifestation of Graves' disease. So far, its etiology remains enigmatic. Optimal therapeutic choices for both GO and Graves' disease are still controversial among endocrinologists, radiologists, ophthalmologists and surgeons. Mild GO may improve spontaneously and only require general measures to control symptoms, whereas moderate to severe GO will require medical treatment.<sup>6</sup> More importantly, patients with GO often suffer from psychological problems which are important determinants of quality of life, particularly during the early days after the diagnosis.<sup>7</sup> Early diagnosis, accurate assessment and timely treatment are essential to improving the outcome. Internationally accepted consensus or guidelines for GO management are still lacking, especially in China. Several previous surveys have elucidated and addressed controversies regarding the management of GO and coexisting hyperthyroidism in Europe and Latin-America. Therefore, we herein conducted a questionnaire survey targeting members of CSE in China. As we anticipated, the overwhelming majority of respondents would welcome the publication of practice guidelines for GO management.

A case of a 65-year-old female patient was used in the survey. Her visual acuity was normal and fundoscopy showed normal optic disks. However, she complained that colours appeared less bright than before, which indicated that she was probably having early optic nerve compression.<sup>3</sup> Almost two thirds of European respondents would urgently refer this GO patient to an ophthalmologist because of the symptoms.<sup>3</sup> On the contrary, the vast majority of Chinese endocrinologists in the present survey replied that the patient should be further investigated by hospitalization, while only a few respondents would refer her to an ophthalmologist during her first visit. Most likely, this significant difference is due to the fact that most Chinese endocrinologists would consider consulting an

ophthalmologist while the patient is hospitalized. The other explanation could be that some respondents may lack the recognition of the disease seriousness.

For patients with mild GO, selenium administration significantly improved quality of life, reduced ocular involvement, and slowed disease progression.<sup>8</sup> Moderate to severe GO can be effectively treated with glucocorticoids, orbital irradiation, or both. High-dose intravenous glucocorticoids should be immediately administered to patients with optic neuropathy.<sup>9</sup> This is likely to be well accepted by endocrinologists from Europe and Latin-America as well as from China. More than 70% of respondents chose intravenous glucocorticoids as the first-line therapy for the patient.

The duration and dose of glucocorticoid treatment have always been contentious. Zang et al<sup>5</sup> in 2011 identified all randomized and uncontrolled trials, consensus statement, systematic reviews, and meta-analyses to investigate the efficacy and adverse effects of intravenous glucocorticoids therapy in GO. They found that the current first-line treatment for active, moderate-to-severe GO was a 12-week course of high-dose intravenous glucocorticoid pulses. When compared with the oral glucocorticoid group, patients in the 12-week intravenous glucocorticoid group had a higher treatment response at three months (72% vs. 49%,  $P < 0.001$ ).<sup>10</sup> Overall, the response rate of this regimen is approximately 80%.<sup>5</sup> The efficacy of the regimen is also well recognized by nearly half of the respondents in our study. Meanwhile, more than one third chose the second 3-day course approach in the questionnaire. Indeed, improvement of soft tissue swelling and ocular motility was observed in only 29% patients.<sup>11</sup> More than a half of the participants replied that the cumulative dose should not exceed 8 g in one single course, which was also strongly recommended by Zang et al. Intravenous glucocorticoids have been thought to have a statistically significant advantage over oral treatment and cause significantly fewer adverse events.<sup>12,13</sup> Recently, a questionnaire survey among members of the European Thyroid Association revealed that glucocorticoids were preferentially administered intravenous for the treatment of GO in Europe, but daily or alternate day intravenous glucocorticoids were also associated with severe adverse effects more frequently, including fatal cases.<sup>14</sup> Further training is required for clinicians on the standardized use of glucocorticoids for the management of GO.

An association between radioiodine therapy for hyperthyroidism and GO was found recently. Radioiodine therapy for hyperthyroidism was followed by statistically significant increases in the ocular manifestations of GD when compared with surgical

thyroidectomy and ATDs treatment.<sup>15,16</sup> Nowadays, radioiodine is considered as the first-line treatment for Graves' Disease in many institutions, particularly in the United States. In the present survey, the proportion of Chinese respondents preferring radioiodine therapy for hyperthyroidism in the case was significantly higher than that of European and Latin-American. However, some studies found that radioiodine therapy could induce onset or progression of GO in approximately 15–20% patients,<sup>17</sup> especially when they had a history of cigarette smoking.<sup>18</sup>

Glucocorticoids prophylaxis is highly effective in preventing deterioration of eye disease in patients with pre-existing ophthalmopathy compared with radioiodine therapy without glucocorticoids.<sup>19</sup> It was recommended by almost two thirds of Chinese respondents in our study. Among them, however, the recommended dose of prophylactic glucocorticoids varied significantly. Lai et al<sup>20</sup> demonstrated that lower doses of oral prednisone (about 0.2 mg/kg bw or 0.3–0.5 mg/kg bw for 6-week) were effective to prevent GO exacerbation without the adverse effects of high-dose intravenous glucocorticoids.

Some limitations of the present study warrant discussion. The sample size is relatively small. Particularly, we didn't collect information on clinical variables in the questionnaire. The active or inactive phase of GO, iatrogenic Cushing's Syndrome, diabetes and a younger age may affect treatment choices of respondents. In addition, the 124 responders who completed this questionnaire survey do not represent all Chinese endocrinologists. A comprehensive investigation of a large sample of endocrinologists is required.

In conclusion, the results of this questionnaire survey confirmed that there is still no consensus regarding to the optimal management of GO among CSE members. A number of disagreements on GO management exist among endocrinologists from Europe, Latin-America, and China. The establishment of practice guidelines for GO management is urgently needed. Further training and education of thyroid specialists are required for the management of the disease.

### Conflicts of interest

The authors have nothing to disclose.

### Acknowledgments

We are grateful to Drs. Guang Ning and Weiping Teng for their support in this survey during the CSE annual meeting. This work was supported by a grant

from the National Natural Science Foundation of China (No. 81200577).

### References

- Lazarus JH. Epidemiology of Graves' orbitopathy (GO) and relationship with thyroid disease. *Best Pract Res Clin Endocrinol Metab.* 2012;26:273–279.
- Ponto KA, Merkesdal S, Hommel G, Pitz S, Pfeiffer N, Kahaly GJ. Public health relevance of Graves' orbitopathy. *J Clin Endocrinol Metab.* 2013;98:145–152.
- Perros P, Baldeschi L, Boboridis K, et al. A questionnaire survey on the management of Graves' orbitopathy in Europe. *Eur J Endocrinol.* 2006;155:207–211.
- Ramos HE, Diehl LA, Camacho CP, Perros P, Graf H. Management of Graves' orbitopathy in Latin America: an international questionnaire study compared with Europe. *Clin Endocrinol (Oxf).* 2008;69:951–956.
- Zang S, Ponto KA, Kahaly GJ. Clinical review: intravenous glucocorticoids for Graves' orbitopathy: efficacy and morbidity. *J Clin Endocrinol Metab.* 2011;96:320–332.
- Marcocci C, Marino M. Treatment of mild, moderate-to-severe and very severe Graves' orbitopathy. *Best Pract Res Clin Endocrinol Metab.* 2012;26:325–337.
- Coulter I, Frewin S, Krassas GE, Perros P. Psychological implications of Graves' orbitopathy. *Eur J Endocrinol.* 2007;157:127–131.
- Marcocci C, Kahaly GJ, Krassas GE, et al. Selenium and the course of mild Graves' orbitopathy. *N Engl J Med.* 2011;364:1920–1931.
- Marcocci C, Altea MA, Leo M. Treatment options for Graves' orbitopathy. *Expert Opin Pharmacother.* 2012;13:795–806.
- Aktaran S, Akarsu E, Erbagci I, Araz M, Okumus S, Kartal M. Comparison of intravenous methylprednisolone therapy vs. oral methylprednisolone therapy in patients with Graves' ophthalmopathy. *Int J Clin Pract.* 2007;61:45–51.
- Ng CM, Yuen HK, Choi KL, et al. Combined orbital irradiation and systemic steroids compared with systemic steroids alone in the management of moderate-to-severe Graves' ophthalmopathy: a preliminary study. *Hong Kong Med J.* 2005;11:322–330.
- Tanda ML, Bartalena L. Efficacy and safety of orbital radiotherapy for graves' orbitopathy. *J Clin Endocrinol Metab.* 2012;97:3857–3865.
- Soeters MR, van Zeijl CJ, Boelen A, et al. Optimal management of Graves orbitopathy: a multidisciplinary approach. *Neth J Med.* 2011;69:302–308.
- Marcocci C, Watt T, Altea MA, et al. Fatal and non-fatal adverse events of glucocorticoid therapy for Graves' orbitopathy: a questionnaire survey among members of the European Thyroid Association. *Eur J Endocrinol.* 2012;166:247–253.
- Bartalena L, Marcocci C, Bogazzi F, et al. Relation between therapy for hyperthyroidism and the course of Graves' ophthalmopathy. *N Engl J Med.* 1998;338:73–78.
- Sisson JC, Schipper MJ, Nelson CC, Freitas JE, Frueh BR. Radioiodine therapy and Graves' ophthalmopathy. *J Nucl Med.* 2008;49:923–930.
- Hegedus L, Bonnema SJ, Smith TJ, Brix TH. Treating the thyroid in the presence of Graves' ophthalmopathy. *Best Pract Res Clin Endocrinol Metab.* 2012;26:313–324.
- Traisk F, Tallstedt L, Abraham-Nordling M, et al. Thyroid-associated ophthalmopathy after treatment for Graves' hyperthyroidism with antithyroid drugs or iodine-131. *J Clin Endocrinol Metab.* 2009;94:3700–3707.

19. Acharya SH, Avenell A, Philip S, Burr J, Bevan JS, Abraham P. Radioiodine therapy (RAI) for Graves' disease (GD) and the effect on ophthalmopathy: a systematic review. *Clin Endocrinol (Oxf)*. 2008;69:943–950.
20. Lai A, Sassi L, Compri E, et al. Lower dose prednisone prevents radioiodine-associated exacerbation of initially mild or absent graves' orbitopathy: a retrospective cohort study. *J Clin Endocrinol Metab*. 2010;95:1333–1337.

Edited by Wei-Zhu Liu