

# Thyroid-associated orbitopathy in patients with thyroid carcinoma

## A case report of 5 cases

Peng Yu, MD<sup>a</sup>, Siyue Liu, MD<sup>a</sup>, Xinrong Zhou, MD, PhD<sup>a</sup>, Teng Huang, MD<sup>a</sup>, Yaling Li, MD<sup>a</sup>, Hong Wang, PhD<sup>b</sup>, Gang Yuan, MD, PhD<sup>a,\*</sup>

### Abstract

**Rationale:** Thyroid-associated orbitopathy (TAO) is most often seen in patients with autoimmune thyroid disease. Data about TAO occurred in patients with thyroid carcinoma are rare. We give a report of 5 patients to present the clinical characteristics, treatment, and prognosis of this type of case.

**Patient concerns:** Five thyroid carcinoma patients presented with orbitopathy. Among them, two patients (patient 1 and 4) were hyperthyroid and TSH receptor antibody (TRAb) positive, two patients (patient 3 and 5) were euthyroid and displayed slightly elevated TRAb titres, one patient (patient 2) was euthyroid and TRAb negative.

**Diagnoses:** They were diagnosed as thyroid carcinoma and TAO.

**Interventions:** Patient 1 underwent total thyroidectomy, intravenous glucocorticoids (GCs) therapy, orbital decompression surgery and oral GCs therapy. Patient 2 and 3 only received total thyroidectomy. Patient 4 received sub-total thyroidectomy and oral GCs therapy. Patient 5 didn't received thyroidectomy and underwent intravenous GCs therapy for 2 courses.

**Outcomes:** Patient 1,2,3 showed an improvement of TAO at the final follow-up. Patient 4,5 showed no improvement of TAO at the final follow-up.

**Lessons:** When TAO present in patients with thyroid nodules, the possibility of thyroid carcinoma should be considered, and the nature of these nodules should be carefully evaluated. In some patients with thyroid carcinoma and TAO, the remission of TAO can be seen post total thyroidectomy. But for other patients, besides thyroidectomy, an adequate dose and course of intravenous GCs treatment and even ocular surgery are also needed.

**Abbreviations:** CAS = clinical activity score, EUGOGO = European Group on Graves' Orbitopathy, FNAB = fine needle aspiration biopsy, GCs = glucocorticoids, GO = Graves' ophthalmopathy, IGF-1 = insulin-like growth factor 1, TAO = thyroid-associated orbitopathy, TRAb = TSH receptor antibody, TSH = thyroid stimulating hormone, TSHR = thyroid-stimulating hormone receptor.

**Keywords:** clinical manifestations, prognosis, thyroid carcinoma, thyroid-associated orbitopathy

## 1. Introduction

Thyroid-associated orbitopathy (TAO), also called Graves' orbitopathy (GO), is an autoimmune disorder. The cross-reaction of thyroid-stimulating hormone receptor (TSHR) antigen in the thyroid and orbital fibroblasts plays an essential role in the

pathogenesis of TAO.<sup>[1]</sup> Current study holds the view that the development of TAO involves the participation of environmental, genetic, and immune factors; any factor that triggers the immune response against TSHR expressed on orbital fibroblasts may initiate the disease process.<sup>[2]</sup> Traditionally, TAO is most often seen in patients with Graves' hyperthyroidism, but it can also present in patients with hypothyroidism and Hashimoto thyroiditis. In addition, it may be observed in individuals exhibiting normal thyroid function with negative thyroid autoantibodies.<sup>[3,4]</sup> Here, we present a case series of 5 patients with thyroid carcinoma presenting with TAO.

## 2. Case presentation

### 2.1. Baseline characteristics

Five patients with thyroid carcinoma and TAO were investigated, and the basic characteristics are presented in Table 1. Of the 5 patients, males occupied a higher proportion compared to females. Their ages ranged from 31 to 57 years with an average of 44.8 years. One patient (patient 5) had a history of smoking. The mean onset time was  $3.4 \pm 1.14$  months. One patient (patient 4) had a past history of hyperthyroidism, and she was diagnosed with hyperthyroidism 5 years ago and underwent a thyroid operation, but the details about this operation were unknown, 2 months before referring to our unit, she underwent subtotal

Editor: Bernhard Schaller.

PY and SL shared first authorship.

This study was approved by the Ethics Committee of Tongji Hospital Affiliated to Huazhong University of Science and Technology.

The authors have no conflicts of interest to disclose.

<sup>a</sup> Department of Internal Medicine, <sup>b</sup> Molecular Diagnostic Laboratory, Tongji Hospital, Huazhong University of Science and Technology, Wuhan, Hubei, China.

\* Correspondence: Gang Yuan, Department of Internal Medicine, Huazhong University of Science and Technology, Wuhan, 430000 Hubei, China (e-mail: Yuangang88@hotmail.com).

Copyright © 2017 the Author(s). Published by Wolters Kluwer Health, Inc. This is an open access article distributed under the Creative Commons Attribution-NoDerivatives License 4.0, which allows for redistribution, commercial and non-commercial, as long as it is passed along unchanged and in whole, with credit to the author.

Medicine (2017) 96:47(e8768)

Received: 15 July 2017 / Received in final form: 24 October 2017 / Accepted: 26 October 2017

<http://dx.doi.org/10.1097/MD.00000000000008768>

**Table 1****Basic characteristics.**

No.	Age	Sex	Smoking	Chief complaint	Past history
Patient 1	31	Male	No	Proptosis, tearing, swelling of eyes for 3 mo	Cholecyst polypus
Patient 2	57	Male	No	Blurred vision for 3 mo	Hypertension for 10 y and taking Irbesartan and Hydrochlorothiazide tablets for treatment; gout for several years
Patient 3	40	Male	No	4 mo of proptosis and 2 y blepharoptosis	Ankylosing spondylitis for 10 y and suspected tuberculosis, taking Humira and Isoniazid for treatment
Patient 4	55	Female	No	Eyelid swelling for 5 mo and subtotal thyroidectomy for 2 mo	Diagnosed as hyperthyroidism 5 years ago and underwent thyroid operation, but the detailed information was unknown; hypertension for 4 y and taking nifedipine for treatment
Patient 5	41	Male	Yes	Proptosis, diplopia and ocular dryness for 4 months	Underwent cholecystectomy 6 years ago

thyroidectomy because of suspicious sonographic findings of a thyroid nodule and taken Euthyrox at a dose of 75 µg postoperation. Except for patient 4, the other patients did not receive any therapy related to thyroid or TAO before referral to our unit.

## 2.2. Thyroid characteristics

At baseline, the thyroid function differs among these patients (Table 2). It should be noted that when patient 4 was first referred to our unit, she had hyperthyroidism; after stopping Euthyrox, she continued to have hyperthyroidism, which indicated that her hyperthyroidism was not caused by excessive use of Euthyrox. As a result, patients 4 and 1 should be classified as the same type; they exhibited the typical feature of Graves' hyperthyroidism: high free T3 and free T4 levels, suppressed TSH level, and positive TRAb. On the contrary, patients 3 and 5 were euthyroid and showed slightly elevated TRAb titers. More interestingly, patient 2 was euthyroid and antibody negative. In summary, we can conclude that in patients with thyroid carcinoma, TAO can be developed in the antibody-negative euthyroid state, antibody-positive euthyroid state, and antibody-positive hyperthyroid state.

The detailed characteristics of the thyroid nodules in these patients are presented in Table 3. All cases had suspicious sonographic features. Four patients underwent fine needle aspiration biopsy (FNAB), and the FNAB results showed malignancy in 3 cases and neoplasm in 1 case. Gene detection was performed in 3 patients; 2 of them had a *BRAF* gene mutation. Four patients underwent thyroidectomy at last, and postoperative pathology confirmed the diagnosis of thyroid carcinoma.

## 2.3. Ocular manifestations of TAO in thyroid carcinoma patients

The ocular characteristics of these patients are presented in Table 4. The diagnosis of TAO was based on the clinical

manifestations and orbital resonance imaging. Orbital carcinoma (including lymphoma, meningioma, and metastatic carcinoma), benign lesions (including cellulitis, inflammatory pseudotumor, myositis, angioma), and some systemic disease (such as IgG4-related disease, amyloidosis, sarcoidosis, vasculitis) were excluded in the differential process. We classified these patients into 3 groups that were stratified based on their thyroid function and the presence of thyroid-associated antibodies. All patients were assessed as moderate-to-severe TAO according to the consensus statement of the European Group on Graves' Orbitopathy (EUGOGO).<sup>[5]</sup>

## 2.4. Follow-up and prognosis

Patient 1 with hyperthyroidism received intravenous glucocorticoids (GCs) therapy at a cumulative dose of 2.5 g (0.5 g each time) before and 1 month post total thyroidectomy and then withdrawal himself. Although his ocular symptoms and clinical activity score (CAS) relieved after treatment, his TAO progressed 4 months later; at that point, his TRAb reached to 15.39 IU/L and CAS score was 6. We gave him a cumulative dose of 2 g intravenous GCs (0.5 g for once and then 0.25 g once weekly for 6 weeks) treatment, his ocular symptoms were temporarily relieved after this treatment and then with a sharp deterioration in eyesight of both side from 0.5 to 0.01, thus he underwent orbital decompression surgery and received oral GCs treatment postocular surgery. At the final follow-up, his eyesight had improved significantly from 0.01 to 0.6 (left) and 0.8 (right), no movement restriction or diplopia were seen, and only a minimal eyelid swelling and eyelid redness existed (initially these signs were marked).

Patients 2 and 3 with euthyroidism received total thyroidectomy and did not receive any other therapies aiming at TAO pre and post total thyroidectomy; they showed a significant improvement in overall assessment of TAO at the final follow-up. For case 2, although a slight eyelid swelling (initially this sign was marked) still

**Table 2****Thyroid function and autoimmunity in each patient at baseline.**

No.	FT4, ng/L	FT3, pg/mL	TSH, µIU/mL	TG, µg/L	TRAb, IU/L	Anti-TG, IU/mL	Anti-TPO, IU/mL
Patient 1	18.83	5.69	0.014	16.36	5.04	10.45	19.43
Patient 2	16.51	2.75	1.029	13.32	0.49	11.37	18.19
Patient 3	13.95	3.67	2.226	11.35	1.69	27.10	54.51
Patient 4	21.26	4.83	<0.005	n.d	>40.00	26.44	9.46
Patient 5	14.76	3.5	0.73	13.71	2.01	23.38	16.48

Reference ranges: FT4, 9.32–17.09 ng/L; FT3, 2.0–4.4 pg/mL; TSH, 0.27–4.2 µIU/mL; TG, 3.5–77 µg/L; TRAb 0–1.58 IU/L; Anti-TG, 0–115 IU/mL; Anti-TPO, 0–34 IU/mL. TRAb = TSH receptor antibody.

**Table 3**  
**Characteristics of the thyroid nodule in each patient.**

No.	Ultrasound	FNAB		Gene detection			Operation	Postoperative pathology
		Lobe	Results	BRAF gene mutation	RET/PTC1 mutation	RET/PTC3 mutation		
Patient 1	A 1.0 × 0.8 cm hypoechoic nodule in the right lobe	Right	Neoplasm	+	—	—	TT	Micropapillary thyroid carcinoma (right)
Patient 2	A 0.6 × 0.4 cm solid lesion in the left lobe, a 0.4 × 0.3 cm hypo-echoic nodule and a 0.5 × 0.4 cm calcification in the right lobe.	Left	Malignancy	n.d	n.d	n.d	TT	Micropapillary thyroid carcinoma (left)
Patient 3	A 1.0 × 0.6 cm inhomogeneous hypo-echoic mass in the isthmus, several inhomogeneous hypo-echoic masses in the right lobe	Right Isthmus	Benign Malignancy	n.d +	n.d —	n.d —	TT	Papillary thyroid carcinoma (right)/micropapillary thyroid carcinoma (left)
Patient 4	Several hypoechoic masses in the right lobe and the isthmus, one of the masses had been calcified	n.d	n.d	n.d	n.d	n.d	Sub-TT	Thyroid microcarcinoma (right)
Patient 5	A 0.5 × 0.3 cm echo-free area in the left lobe, a 0.5 × 0.5 cm inhomogeneous hypoechoic mass in the right lobe	Left	Malignancy	—	—	—	n.d	n.d

n.d=not done, sub-TT=subtotal thyroidectomy, TT=total thyroidectomy.

existed, he showed an improvement of eye motility: initially, he showed limitation of all directions; now he exhibited limitation of upward and outward gaze in the left eye (inconstant), and limitation of downward gaze in the right eye (inconstant). For case 3, he showed no sign of soft-tissue involvement and the movement limitation in his right eye disappeared.

Patient 4 with hyperthyroidism showed no obvious change in the TAO and remained hyperthyroid 2 months after subtotal

thyroidectomy. Then, she was referred to our clinic, because the patient refused to receive intravenous GCs treatment, oral prednisone regimen was given (initial dose of 35 mg per day, 5 mg reduction every two weeks) to treat TAO; meanwhile, methimazole (5 mg per day) was given to control her hyperthyroidism, but no improvement was found at the final follow-up.

Patient 5 with euthyroidism did not undergo thyroidectomy (he refused this due to personal reasons) and received 2 courses'

**Table 4**  
**Patients' ophthalmic characteristics.**

	Antibody-positive hyperthyroid		Antibody-positive euthyroid		Antibody-negative euthyroid
	Patient 1	Patient 4	Patient 3	Patient 5	Patient 2
Upper eyelid retraction	+/-	+/+	+/-	-/-	-/+
Lower eyelid retraction	-/+	+/-	-/-	-/-	+/+
Eyelid lag	+/-	+/-	+/-	-/-	+/+
Spontaneous retrobulbar pain	—	+	—	+	—
Pain on attempted upward or downward gaze	—	—	—	—	—
Swelling of eyelids	+/+	+/+	-/-	+/+	+/+
Redness of eyelids	+/+	-/-	-/-	+/+	-/-
Swelling of caruncle or plica	-/+	-/-	+/-	-/-	-/-
Swelling of conjunctiva	-/-	-/+	-/-	+/+	-/-
Redness of conjunctiva	+/+	-/-	+/-	-/-	-/-
Exophthalmos, mm	17.3/19.2	15/22	20.5/19.1	24.5/24.8	21.8/24.4
Diplopia	+	—	—	+	+(inconstant)
Movement limitation	Normal/downward	Upward/ upward, outward	Upward/normal	Normal	All direction (inconstant)
Vision	0.5/1.0	0.5/0.5	1.0/1.0	1.0/1.0	1.0/0.8
CAS score	4	3	2	4	1
Severity assessment	Moderate-to-severe	Moderate-to-severe	Moderate-to-severe	Moderate-to-severe	Moderate-to-severe

Data present as right/left.  
 CAS = clinical activity score.

intravenous GCs therapy in 2 months (at a dose of 500 mg once every two days, 3 times in one course); his TAO showed no change at the final follow-up. A brief summary of the treatments and outcomes are summarized in Table 5; the outcome of TAO was mainly assessed according to the criteria as used by the EUGOGO and was classified as improvement, deterioration, and no change.<sup>[6]</sup>

### 3. Discussion

Our report presents 5 patients who developed TAO with thyroid carcinoma. Previously, reports about this kind of case were rare; only Yoon et al had reported 5 cases in euthyroid state with positive TRAb.<sup>[7]</sup> In our present cases, besides cases similar to this, there also were 2 cases with TRAb-positive hyperthyroidism and 1 case with an antibody-negative euthyroid state, which were reported for the first time.

The differential diagnose is important for patients presenting with orbitopathy. For our patients, orbital carcinoma, orbital benign lesions, and the possibility of systemic disease-related orbitopathy were all considered and then excluded in the diagnostic process. Moreover, although orbital is not the common sites for metastatic thyroid carcinomas, metastases of thyroid carcinomas to the orbital have been reported.<sup>[8]</sup> Thus, for patients with thyroid carcinoma and TAO, especially those who have lymph node metastasis, this should also be taken into consideration; computed tomography (CT) and magnetic resonance imaging (MRI) scanning can be useful in the diagnostic process, and fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT) is powerful to detect unexpected distant metastases from thyroid carcinomas.<sup>[9]</sup> In our cases, all patients did not show ocular imaging features related to metastases and the 4 patients who had received thyroidectomy did not have lymph node metastasis according to the physiological analysis, so this possibility can also be excluded.

Patients 1 and 4 initially had apparent eye symptoms and the thyroid laboratory examination revealed a Graves' pattern. As a result, their preliminary diagnosis was considered as Graves' disease combined with TAO. Subsequent examination indicated the possibility of thyroid cancer and postoperative pathological examination confirmed it. Graves' disease can coexist with thyroid carcinoma; moreover, in the population-based cohort study, patients with GD have a higher incidence of thyroid cancer than controls.<sup>[10,11]</sup> Therefore, it is entirely possible that thyroid cancer patients exhibit TAO from Graves' disease.

Patients 2, 3, and 5 had euthyroid TAO, which refers to patients who do not have a current or past history of hyperthyroidism.<sup>[12]</sup> Previous study revealed that compared with hyperthyroid TAO patients, euthyroid TAO tends to have

less active, severe clinical manifestations and lower TRAb levels.<sup>[13,14]</sup> In patients with thyroid carcinoma and TAO, some of the above conclusions still hold true; for example, euthyroid group only had a slightly elevated titer of TRAb or within normal range. Despite this, we found that hyperthyroid patients had a marked decrease in eyesight, while the other patients did not exhibit blurred vision.

Except for normal thyroid function, patient 2 also had a very special feature: his TRAb was negative. In ordinary TAO patients, this type also exists. It is widely accepted that TRAb combines with fibrocytes TSHR and then initiates destructive biological effects, including secretion of inflammatory cytokines and chemokines, enhanced hyaluronic acid production, and adipogenesis, which contributes to the formation of TAO.<sup>[2]</sup> However, current study indicated that in addition to the participation of TSHR in the pathogenesis of TAO, factors such as insulin-like growth factor 1 (IGF-1) that act through IGF-R can also generate a similar biological effect<sup>[15]</sup>; we cannot exclude the possibility that the increase of certain bioactive molecules locally or systemically may trigger the TAO pathogenesis process.

From the retrospective analysis of the treatments and prognoses of these patients, we found the following: total thyroidectomy alone may improve TAO manifestations in some patients, and patients 2 and 3 showed an improvement post thyroidectomy. Intravenous GCs treatment remains effective against TAO in thyroid carcinoma patients. For patients in whom thyroidectomy alone did not give an improvement to TAO, intravenous GCs therapy can be helpful. In very severe cases, additional treatment, such as orbital decompression surgery, tended to be an effective method for treating TAO. Subtotal thyroidectomy may not be an ideal method to treat hyperthyroidism in patients who developed thyroid carcinoma with Graves' disease. Patient 4 remained hyperthyroid following subtotal thyroidectomy, which can affect the thyroid immunity and is not favorable for the alleviation of TAO.<sup>[16]</sup>

GCs are an effective means for treating TAO because of their anti-inflammatory and immunosuppressive actions, and they remain effective in patients with thyroid carcinoma, but we need to pay attention to some points in managing this patient type. First, patient 4 used oral GCs and showed no response to this treatment, indicating the importance of intravenous GCs as the first-line treatment. Studies have indicated that intravenous GCs are significantly better than the oral route in reducing CAS and this route has a lower rate of adverse events with a significantly higher response rate.<sup>[17,18]</sup> Second, the dose and course of intravenous GCs is closely associated with the outcome of TAO; Bartalena et al<sup>[19]</sup> conducted a randomized clinical trial in patients with moderate to severe and active GO; they divided patients into 3 groups and gave cumulative dose of 2.25, 4.98, or

**Table 5**

#### Treatment and prognosis of each patient.

Patient	Preoperation	Operation	Postoperation	Follow-up period, mo	CAS scores	Outcome
Patient 1	i.v. GCs	TT	Levothyroxine, i.v. GCs, decompression surgery, oral GCs	21	2	Improvement
Patient 2	—	TT	Levothyroxine	15	1	Improvement
Patient 3	—	TT	Levothyroxine	17	0	Improvement
Patient 4	—	Sub-TT	Oral GCs, methimazole	8	3	No change
Patient 5*	—	—	—	8	3	No change

At last follow-up, all patients were in euthyroid state.

The follow-up period was defined as the period from the date of discharge of their first visit to the final follow-up.

CAS = clinical activity score, i.v. GCs = intravenous glucocorticoids, sub-TT = subtotal thyroidectomy, TT = total thyroidectomy.

\* Case 5 did not receive thyroidectomy and only underwent intravenous GCs treatment.

7.47g GCs in 12 weekly infusions. They found that the 2.25g group led to the lowest improvement in the overall assessment of TAO at 12 and 24 weeks. In addition, among patients whose GO had improved at 12 weeks, the relapse rate was highest (40 vs 21 and 33% using 4.98 and 7.47g, respectively) in the 2.25g group at 24 weeks.<sup>[19]</sup> Patient 1 initially only received 2.5g of GCs and then stopped treatment for personal reasons; thus, his progression of TAO in later times was largely due to the insufficient dose. As the 7.47g dose of GCs was associated with a higher incidence of adverse events, at least 4.5 to 5g should be used in patients with moderate to severe and active GO.<sup>[5,19]</sup> Third, additional treatment should be considered in some complicated situations. In patient 1, when his TAO had worsened and presented as sight-threatening, orbital decompression surgery was performed, and he achieved final remission of TAO with this surgery. This indicated that orbital decompression was also an effective and safe treatment in patients with thyroid carcinoma; through decompression, the hyperintraorbital pressure can be reduced and venous outflow can be increased, alleviating exophthalmos, eye lid retraction, soft tissue congestion as well as improving eyesight.<sup>[20,21]</sup>

#### 4. Conclusion

We showed the clinical characteristics, treatment, and prognosis of TAO in thyroid carcinoma patients with different thyroid functions and immune states. This suggests that the possibility of thyroid carcinoma should be considered when TAO symptoms present in patients with thyroid nodules. For some patients, they get an improvement of TAO post total thyroidectomy; however, for other patients, besides thyroidectomy, adequate intravenous GC treatment and even ocular decompression surgery are also needed. As patients with thyroid carcinoma and TAO are very rare, we just give a preliminary study about this through case report, and a multicenter observational study is needed to confirm our results and give further study of this topic.

#### References

- [1] Bahn RS, Dutton CM, Natt N, et al. Thyrotropin receptor expression in Graves' orbital adipose/connective tissues: potential autoantigen in Graves' ophthalmopathy. *J Clin Endocrinol Metab* 1998;83:998–1002.
- [2] Bahn RS. Current insights into the pathogenesis of Graves' ophthalmopathy. *Horm Metab Res* 2015;47:773–8.
- [3] Bartley GB, Fatourehchi V, Kadrmas EF, et al. Clinical features of Graves' ophthalmopathy in an incidence cohort. *Am J Ophthalmol* 1996;121:284–90.
- [4] Cakir M. Euthyroid Graves' ophthalmopathy with negative autoantibodies. *J Natl Med Assoc* 2005;97:1547–9.
- [5] Bartalena L, Baldeschi L, Boboridis K, et al. The 2016 European Thyroid Association/European Group on Graves' Orbitopathy Guidelines for the management of Graves' orbitopathy. *Eur Thyroid J* 2016;5:9–26.
- [6] Stan MN, Salvi M. Management of endocrine disease: rituximab therapy for Graves' orbitopathy: lessons from randomized control trials. *Eur J Endocrinol* 2017;176:R101–r109.
- [7] Yoon JS, Lew H, Park JS, et al. Papillary thyroid carcinoma with thyroid-associated orbitopathy in a euthyroid state. *Ophthal Plast Reconstr Surg* 2007;23:187–91.
- [8] Besic N, Luznik Z. Choroidal and orbital metastases from thyroid cancer. *Thyroid* 2013;23:543–51.
- [9] Sandu N, Popperl G, Toubert ME, et al. Molecular imaging of potential bone metastasis from differentiated thyroid cancer: a case report. *J Med Case Rep* 2011;5:522.
- [10] Chen YK, Lin CL, Chang YJ, et al. Cancer risk in patients with Graves' disease: a nationwide cohort study. *Thyroid* 2013;23:879–84.
- [11] Shu X, Ji J, Li X, et al. Cancer risk in patients hospitalised for Graves' disease: a population-based cohort study in Sweden. *Bri J Cancer* 2010;102:1397–9.
- [12] Kazuo K, Fujikado T, Ohmi G, et al. Value of thyroid stimulating antibody in the diagnosis of thyroid associated ophthalmopathy of euthyroid patients. *Br J Ophthalmol* 1997;81:1080–3.
- [13] Eckstein AK, Losch C, Glowacka D, et al. Euthyroid and primarily hypothyroid patients develop milder and significantly more asymmetrical Graves ophthalmopathy. *Br J Ophthalmol* 2009;93:1052–6.
- [14] Jang SY, Lee SY, Lee EJ, et al. Clinical features of thyroid-associated ophthalmopathy in clinically euthyroid Korean patients. *Eye (London, England)* 2012;26:1263–9.
- [15] Pritchard J, Han R, Horst N, et al. Immunoglobulin activation of T cell chemoattractant expression in fibroblasts from patients with Graves' disease is mediated through the insulin-like growth factor I receptor pathway. *J Immunol (Baltimore, Md: 1950)* 2003;170:6348–54.
- [16] Marcocci C, Bartalena L, Bogazzi F, et al. Relationship between Graves' ophthalmopathy and type of treatment of Graves' hyperthyroidism. *Thyroid* 1992;2:171–8.
- [17] Stiebel-Kalish H, Robenshtok E, Hasanreisoglu M, et al. Treatment modalities for Graves' ophthalmopathy: systematic review and meta-analysis. *J Clin Endocrinol Metab* 2009;94:2708–16.
- [18] Zang S, Ponto KA, Kahaly GJ. Clinical review: intravenous glucocorticoids for Graves' orbitopathy: efficacy and morbidity. *J Clin Endocrinol Metab* 2011;96:320–32.
- [19] Bartalena L, Krassas GE, Wiersinga W, et al. Efficacy and safety of three different cumulative doses of intravenous methylprednisolone for moderate to severe and active Graves' orbitopathy. *J Clin Endocrinol Metab* 2012;97:4454–63.
- [20] Onaran Z, Konuk O, Oktar SO, et al. Intraocular pressure lowering effect of orbital decompression is related to increased venous outflow in Graves orbitopathy. *Curr Eye Res* 2014;39:666–72.
- [21] Fichter N, Guthoff RF, Schittkowski MP. Orbital decompression in thyroid eye disease. *ISRN Ophthalmol* 2012;2012:739236.