·**Clinical Research**·

CT features of exophthalmos in Chinese subjects with thyroid–associated ophthalmopathy

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Abstract

• **AIM:** To investigate computed tomography (CT) features of exophthalmos in Chinese subjects with thyroid–associated ophthalmopathy (TAO).

• **METHODS:** A total of 605 eyes of 325 patients with exophthalmos due to TAO were classified as grade I (mild exophthalmos) or II (severe exophthalmos) based on orbital CT imaging. The increased orbital volume features, such as changes from extraocular muscles, orbital fat, or both, were analyzed.

• **RESULTS:** A total of 605 eyes were analyzed, among them 62.98% presented grade I exophthalmos, while 36.02% showed grade II exophthalmos. In grade I, 56.69% showed orbital fat change, and in grade II, 89.29% exhibited extraocular muscle enlargement.

• **CONCLUSION:** Orbital fat and extraocular muscle enlargement are likely to be observed on CTs of subjects with mild and severe exophthalmos, respectively. Our results suggest that CT findings may guide TAO clinical therapy recommendations and prognosis.

• **KEYWORDS:** thyroid-associated ophthalmopathy (TAO); computed tomography (CT); exophthalmos

INTRODUCTION

Thyroid-associated ophthalmopathy (TAO) is an inflammatory condition of the orbital tissues that is commonly associated with thyroid disorders. Clinical features of TAO include eyelid retraction, upper eyelid lag, exophthalmos, limited ocular movements, and diplopia. Severe exophthalmos can result in exposure keratitis, corneal perforation, and, ultimately, blindness. The pathological findings associated with TAO are glycosaminoglycan (GAG) deposition (accompanied by swelling due to the hydrophilic capacity of these macromolecules), fibrosis of the extraocular muscles, and adipogenesis in the orbit [1-4]. Collectively, these changes lead to exophthalmos, which ultimately causes severe vision loss due to corneal ulcers or optic nerve compression or stretching. Early detection of exophthalmos is essential for achieving good outcomes in TAO patients.

The widespread availability of magnetic resonance imaging (MRI) and computed tomography (CT) have made early detection of exophthalmos possible, and the imaging presentation of TAO can precede clinical signs of hyperthyroidism and significant changes in laboratory tests; therefore, most researchers and clinicians suggest that abnormal imaging findings may be a sign of early thyroid disease [5,6]. However, how orbital fat changes manifest and where extraocular muscle enlargement distributes in Chinese TAO patients is unknown. The goal of this study was to characterize the orbital CT features of Chinese subjects with TAO.

SUBJECTS AND METHODS

Diagnosis of TAO We employed the American Thyroid Association (ATA) classification for TAO diagnosis [7]. Briefly, patients exhibited lid retraction with one or more signs of thyroid dysfunction, exophthalmos (20mm or more by Hertel measurements), extraocular muscle enlargement, or optic neuropathy [8]. In the absence of lid retraction, laboratory evidence of thyroid dysfunction and at least one of the other signs were sufficient for a diagnosis of TAO.

Exclusion criteria Subjects were excluded if they presented with a concurrent illness that caused an increase in orbital volume (*i.e.*, lacrimal gland prolapse, acute inflammation due to infection, orbital tumor, *etc*), and patients with only coronal or axial CT were also excluded.

Subjects A total of 325 subjects (605 eyes) with evidence of exophthalmos and orbital CT scans taken between March 2010 and March 2012 were included in the study.
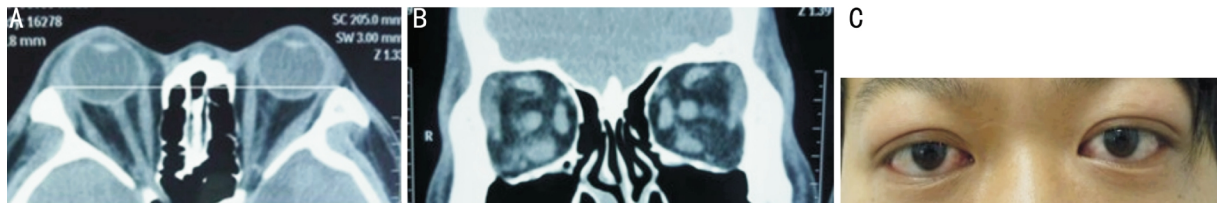
Figure 1 A 23-year-old male exhibited exophthalmos for 2 years and had a history of hyperthyroidism CT scans revealed grade I exophthalmos with enlargement of extraocular muscles and increased orbital fat. A: axial scan; B: coronal scan.
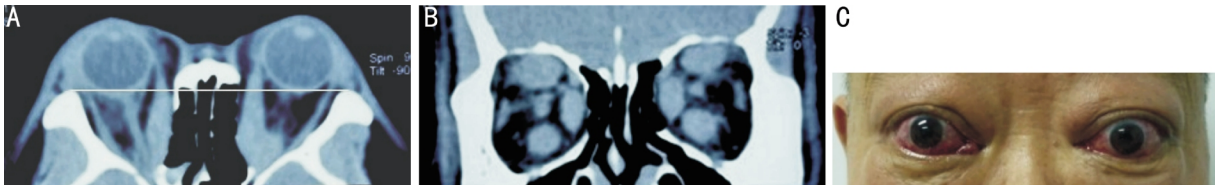
Figure 2 A 60-year-old male with euthyroidism presented with conjunctival congestion and a 6-month history of exophthalmos CT scans revealed grade II exophthalmos with four enlarged ocular muscles. Orbital volume was increased, mainly due to extraocular muscle enlargement. A: axial scan; B: coronal scan.
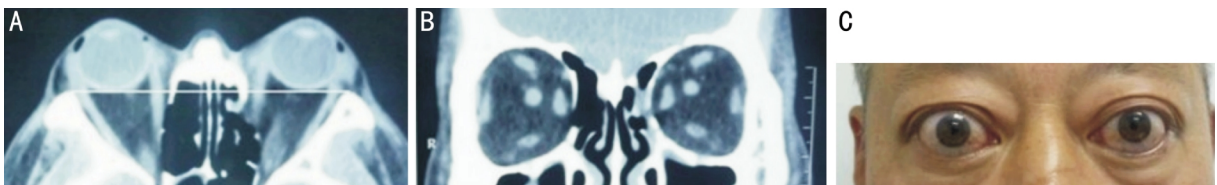
Figure 3 A 48-year-old male with euthyroidism presented with a 12-year history of exophthalmos CT scans displayed grade II exophthalmos, mainly from increased orbital fat A: axial scan; B: coronal scan.

CT imaging Philips Brilliance spiral 64-CT equipment was used. Axial and coronal CT scans were performed on 325 subjects with the following parameters: 120kV, 150mm, 512×512 matrix. Images were taken with slice thicknesses of 2.5mm, slice intervals of 2.5mm, and sequential scanning. The window width was set to 300-400Hu, and the window level was set to 35-50Hu. The major morphological diagnostic criteria of extraocular muscle enlargement include spindle-like spreading of the rectus muscles without tendon involvement, optic nerve compression in the orbital apex, and the absence of any space occupying intra-orbital processes [9]. Fat has a lower density than other tissues, and so appears black in contrast to muscles, optic nerve, and bony structures on CT [10]. The normal CT value of fat tissue is about 50-100Hu or lower, and values that exceeded this range were defined as increased fat density in our study.

Exophthalmos classification by CT The CT scan containing the maximum diameter slice was selected, and the interzygomatic line was used as a reference (Figures 1A, 2A, and 3A). If over half the axial length of the eye was posterior to the interzygomatic line, exophthalmos was not present. If more than two-thirds of the axial length of the eye protruded over the interzygomatic line, the subject was diagnosed with exophthalmos. If the interzygomatic line located between one-half and two-thirds, the case was followed up, or the measurement was compared with the other eye. Grade I (mild, Figure 1) exophthalmos was defined when the posterior eye segment was located posterior to the interzygomatic line, and grade II (severe, Figure 2 and 3) was diagnosed when the posterior eye segment was located anterior to the interzygomatic line.

Statistical Analysis Data was analyzed with SPSS 15.0 statistical software. Age was compared by variance analysis, and ratios were compared with chi-squared tests. For all statistical analyses, differences were considered significant when $P < 0.05$.

RESULTS

A total of 605 eyes of 325 patients (153 males and 172 females) with exophthalmos were analyzed. Overall, 45 and 280 patients had single and bilateral exophthalmos, respectively. Subject age ranged from 5 to 80 years, with a mean age of 46 years. TAO course ranged from 1 month to 20 years, with mean disease duration of 30.3 months. Most patients had a history of hyperthyroidism, hypothyroidism, or other thyroid dysfunction, but 20% (65/325) had no history of thyroid disease or dysfunction.

CT Findings

Number of extraocular muscles involved The number of extraocular muscles involved in grade I and II exophthalmos is shown in Table 1. We found that grades I and II exophthalmos accounted for 62.98% (381/605) and 37.02% (224/605), respectively. There was a statistically significant difference between the two groups ($\chi^2 = 35.104$, $P = 0.000$).

Extraocular muscles involved The number of extraocular muscles involved is listed in Table 2. In grade I, exophthalmos involved extraocular muscles in descending

Table 1 Number of extraocular muscle enlargements in grades I and II exophthalmos $n(\%)$

Groups	Number of extraocular muscle groups enlarged					Total
	0	1	2	3	4	
Grade I	113(29.67)	56(14.70)	43(11.29)	62(16.27)	107 (28.08)	381
Grade II	24(10.71)	30(13.39)	26(11.61)	43(19.20)	101(45.09)	224
χ^2	28.902	0.197	0.014	0.841	18.082	
P	0.000	0.657	0.905	0.359	0.000	

Table 2 Number of involved extraocular muscles in grades I and II exophthalmos $n(\%)$

Severity	Superior rectus	Inferior rectus	Medial rectus	Lateral rectus	Total
Grade I	211 (55.38)	216 (56.69)	199 (52.23)	130 (34.12)	381
Grade II	152 (67.86)	188 (83.93)	165 (73.66)	110 (49.11)	224
χ^2	9.15	47.17	27.03	13.24	
P	0.002	0.000	0.000	0.000	

Table 3 Orbital fat volume increase in grade I and II exophthalmos $n(\%)$

Severity	Increased orbital fat	No change in orbital fat	Total
Grade I	216(56.69)	165(43.31)	381
Grade II	90(40.18)	134(59.82)	224
Total	306(50.00)	299(50.00)	605

Table 4 Rate of extraocular muscle enlargement and orbit fat increase in grades I and II exophthalmos $n(\%)$

Groups	None	Extraocular muscle enlargement	Orbital fat increase	Both	Total
Grade I	12(3.15)	153(40.16)	67(17.59)	149(39.10)	381
Grade II	2(0.89)	132(58.93)	33(14.73)	57(25.45)	224
χ^2	2.258	19.949	0.832	11.724	
P	0.1329	0.000	0.362	0.001	

rank, as follows: inferior rectus, superior rectus, medial rectus, and lateral rectus. For grade II, the involved muscles (descending order) were: inferior rectus, medial rectus, superior rectus, and lateral rectus. Regardless of TAO severity, inferior rectus muscle enlargement occurred most frequently in both.

Orbit fat volume increase Table 3 shows that 56.69% patients with grade I exophthalmos and 40.18% with grade II exhibited orbital fat volume increase, suggesting that orbital fat might play a more important role in mild exophthalmos (χ^2=15.397, P=0.000).

Relative contributions of extraocular muscle enlargement and orbital fat The data presented in Table 4 indicate that extraocular muscle enlargement was more likely to occur in grade II exophthalmos, while combined changes in both orbital fat and extraocular muscles contributed more to grade I exophthalmos.

DISCUSSION

Radiological diagnosis is an important component of TAO management. It is not unusual for TAO patients with exophthalmos to exhibit euthyroidism[6]; in our study, 20% of subjects exhibited euthyroidism. Thus, it is valuable to elucidate the significance of specific radiological findings to provide accurate diagnoses or suggest subsequent testing to rule out thyroid dysfunction. MRI is a valuable tool that can be used to detect morphological and water content changes in the extraocular muscles of TAO patients. Orbital soft tissue edema can also be accessed *via* MRI through observation of extraocular muscle changes[11,12]. However, because orbital fat can disrupt the images, fat-suppression technology must be used, leading to high costs and complex MRI protocols. In contrast, CT is more sensitive in identifying enlarged extraocular muscles [13]. Axial and coronal CT scanning is non-invasive, simple, fast, and cost effective. Findings on CT scanning may include muscle belly enlargement, apparent increase in orbital fat volume, and crowding of the optic nerve at the orbital apex. For these reasons, CT imaging should be considered first during diagnostic evaluation of TAO. Exophthalmos is usually measured with a Hertel exophthalmometer. The average measurement is 13.64mm [14], and the difference between bilateral eye protrusions should be within 2mm. A diagnosis of exophthalmos can be made when the Hertel measurement exceeds 20mm. However, this method has poor reproducibility due to exophthalmometer variance, orbital interval, instrument operator bias, and variance of eye diameter as a result of ametropia. The 6-mm interval between normal and abnormal margins further decreases the precision of clinical diagnosis of exophthalmos of TAO. CT imaging is advantageous because it depicts a clear outline of the eye globe that allows precise measurements. In addition, it shows the relationship between the eye and the orbital cavity, making it possible to evaluate internal orbital structures, including extraocular muscle and fat tissues.

Many groups have proposed CT criteria for the diagnosis of exophthalmos. Ozgen *et al* [15] measured the distance between

the posterior eye and the interzygomatic line drawn between the right and left lateral orbital margins and reported a normal range of 5.9 to12.8mm, with a mean of 9.4mm. Zhang *et al* [16,17] measured the distance between the cornea and the interzygomatic line in a group of normal Chinese subjects and described a range of 9.9-14.1mm, with a mean value of 12.4mm. They further classified exophthalmos into grade I (mild) and grade II (severe). Using this method, we identified 381 eyes (62.98%) and 224 eyes (36%) with grades I and II exophthalmos, respectively.

TAO exophthalmos results from extraocular muscle enlargement, increased orbital fat, orbital soft tissue edema, and contraction of Müller's muscle. Changes in extraocular muscle size and increased amounts of orbital fat can be assessed with CT. Ozgen *et al* [18] reported that TAO was diagnosed by CT imaging analysis in 79% of subjects with Graves' disease, demonstrating that CT imaging is a more sensitive diagnostic method than clinical examination. In our study, TAO-associated changes, such as abnormal eye position, enlarged extraocular muscles, and exophthalmos, were present in 20% of subjects with euthyroidism. Therefore, changes identified on orbital CT imaging might be useful in making an efficient and accurate diagnosis of TAO, even in patients with euthyroidism.

The contribution of extraocular muscle enlargement to exophthalmos can be easily remembered with the "I'M SLO" mnemonic, which lists extraocular muscle involvement (in decreasing order of frequency) as inferior, medial, superior, and lateral rectus muscles, followed by the oblique muscle. For our patients, this mnemonic was true for grade II, but not for grade I exophthalmos. In mild cases of exophthalmos, the superior rectus muscle was more commonly involved than the medial rectus muscle. Peyster *et al* [19] showed that there was an increased amount of orbital fat in patients with Graves' eye disease and suggested that excessive orbital fat influenced exophthalmos. Similarly, Nishida *et al* [20] hypothesized that orbital fat had more of an effect than increased extraocular muscle volume. Regensburg *et al* [21] demonstrated that the mean orbital fat density was higher in patients with Graves' ophthalmopathy than in the normal population, and found a negative correlation between orbital fat density and orbital fat volume. We found that although orbital fat changes and muscle enlargement both lead to increased orbital volume, orbital fat change was more important in grade I than in grade II.

We found that extraocular muscle enlargement accounted for the orbital volume increase in 40% and 58.9% of eyes with mild and severe exophthalmos, respectively. Conversely, orbital fat change was observed in 39.1% of grade I, but only 25.4% of grade II exophthalmos.

In general, our study indicates that in Chinese subjects with TAO, orbital fat involvement seems to be the major factor in mild exophthalmos, whereas severe exophthalmos appears to be more related to rectus muscle enlargement. However, further study is required.

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