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Original research

Ultrasonographic motion analysis of lower eyelid compartments in patients with chronic thyroid associated ophthalmopathy

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Abstract

Purpose: To present the qualitative and quantitative ultrasonographic findings of lower eyelid compartments in patients with chronic thyroid associated ophthalmopathy (TAO) compared to normal subjects.
Methods: In a prospective study, dynamic and static ultrasonographic investigation, applying high resolution (15 MHz) ultrasound was performed to assess the lower eyelid, in 15 TAO patients that were in chronic phase and 10 normal subjects. The thickness and echogenisity of dermis, orbicular oculi muscle, lower eyelid retractor muscle, lower eyelid fat pads, and their qualitative relationships during vertical excursion of the globe were evaluated in static and dynamic investigation. Correlation of ultrasonic and clinical findings was evaluated.
Results: The mean age of the patients was 41.82 ± 7.4 years, and the controls were age-matched (mean age, 42.8 ± 5.6 years). Mean proptosis of the involved eyes was 3.3 mm, and mean lower lid retraction was 2.4 mm in chronic TAO group. Pattern of fat motion was blocky in chronic TAO patients compared to normal jelly motion of the fat in normal cases. In analyzing the range of motion, the difference was significant in the motion of both superficial and deep fat pockets between the two groups ($P < 0.001$). Limitation of fat motion correlated both with proptosis and lower eyelid retraction (Pearson correlation coefficient = −0.77 vs −0.43, $P < 0.001$). Fibrotic changes of lower lid fat pads appear in the tissue around the septum on observation. Considering the ultrasound findings, a new staging method is proposed in this study that starts with the appearance of echodense points, getting worse in fine bands, progresses to thick bands and ends in cord formation in the lower lid fat pocket that determines total fibrosis.
Conclusion: Development of a series of static and dynamic changes in ultrasound is related to the clinical findings in chronic phase of TAO. The limitation of motion and fibrotic changes of lower eyelid fat pads were more detectable in cases with a more severe proptosis and lower lid retraction. It is considered that ultrasound findings can be a representative of the severity of involvement in the chronic phase of the TAO.

Keywords: Thyroid associated ophthalmopathy; Lower lid retraction; Ultrasonography; Lower lid fat pads

Introduction

Diagnosis of thyroid associated ophthalmopathy (TAO) is based on the typical ocular signs and symptoms, in the evidence thyroid auto-immunity, and exclusion of other orbital pathologies. More than 25−50% of individuals with Graves' disease have clinical involvement of the eyes.[1] The most

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obvious pathological change within the orbit is the enlargement of extraocular muscles.[2] Also periorbital and infraorbital soft tissue enlargement is a common finding.

Orbital involvement in TAO can be divided into 2 distinct phases: active phase in which the orbit is inflamed, and clinical findings which relate to inflammation including chemosis, injection, and lid edema. Later in the course of the disease, resolution of the inflammation occurs and subsequent fibrosis of the inflamed tissues progress. This phase results in many reported signs and symptoms of chronic TAO including lid lag, proptosis, and strabismus problems such as diplopia and extraocular muscle motion limitation without any finding of active inflammation.

In some chronic TAO patients, development of a scar tissue is insidious. Diagnosis of this slowly progressive process and controlling and cessation of it would help in the prevention of severe fibrotic stage of the disease. There are many studies regarding the application of CT-scan, MRI, and ultrasound in the diagnosis of extraocular muscle enlargement and also changes in orbital fat volume. There are some studies about the changes of fat volume in the pathogenesis of proptosis[3,4] whereas in a recent study, the primary cause of the retraction was proposed to be the proptosis.[5] To our knowledge, this is the first study that uses ultrasound to determine the characteristics of orbital fat in terms of echogenisity and motion behavior in chronic TAO patients. We published a study recently that was performed to assess the motion behavior in lower eyelid fat pockets in 7 normal cases.[6] It raised the question if there is any structural change in the orbital and periorbital area in chronic TAO patients detectable by ultrasonography as this technique is able to discriminate soft tissue changes to a high extent; and if so, is the deviation of ultrasonic parameters from normal values correlated to clinical findings such as degree of ocular movement limitation, diplopia, and lower eyelid retraction and proptosis in chronic TAO patients.

Therefore, a study was designed to evaluate dynamic and static ultrasonographic properties of lower eyelid soft tissue such as septum, retractor muscle, and orbital fat pads in chronic TAO patients, and the values were compared to normal cases. Correlation of these findings with the severity indices of the chronic TAO is also investigated. Detection of such a correlation with clinical findings can help us use a non-invasive no-radiation technique to evaluate the course of the chronic TAO.

Methods

Between September 2010 and February 2011, 15 consecutive patients with the definitive diagnosis of TAO, that were not in the active state of the disease, were recruited in the study. These cases were referred to the Division of Oculoplasty, Jules Stein Eye Institute at UCLA, Los Angeles, USA. Patients were excluded from the study if they had received previous surgical treatment for their orbitopathy. The tenets of the Declaration of Helsinki were followed. For comparison between chronic TAO and normal subjects, 10 healthy volunteers were included in the control group.

All the participants underwent thorough ocular examination. Exophthalmometry and lower lid retraction were measured and recorded. Ultrasonographic evaluation (Logiq p6, GE Healthcare, USA) was performed by a single operator, an expert ophthalmologist, using a 15-MHz probe with linear producer. The scanner operated at a scan rate of 50 frames per second. During the assessment, the eyelids were closed and covered with methyl cellulose medium for optimal signal transmission.

Ultrasonographic examinations were performed with the patient in a semi-supine position. The probe was placed perpendicular to the area of interest and allowed visualization of the lower lid compartments in an area in the mid-sagittal plane that inferiorly extended to the orbital rim. Subjects were instructed to place their eyes in maximum down-gaze and then extreme up-gaze, allowing video recording of the globe in maximum vertical excursion. Static images were extracted and used to characterize eyelid anatomical compartments during various phases of motion. For analysis, Movie MaxTRAQ 2.0 (Innovision systems Inc., Columbiaville, MI, USA) was used.

The tissue echogenisity differences make definite tissue boundaries, and the distance between the two subsequent boundaries is considered thickness.

The thickness and echogenisity of dermis, orbicular oculi muscle, lower eyelid retractor muscle, lower eyelid fat pads, and their qualitative relationships during vertical excursion of the globe were evaluated in static and dynamic investigation. Correlation of ultrasonic and clinical findings was evaluated.

Data were analyzed using SPSS 13.0. Student's *t*-test, one-sample *T* test, and Pearson correlation analysis was applied. *P* values less than 0.05 were considered statistically significant.

Results

A total of 15 patients with chronic TAO and a control group of 10 healthy individuals (10 eyes) were enrolled into the study. The mean age of the patients was 41.82 ± 7.4 years, and the controls were age-matched (mean age, 42.8 ± 5.6 years).

Mean proptosis of the involved eyes was 3.3 mm (range, 2.3−4.3 mm). Mean lower lid retraction was 2.4 mm (range, 1.7−3 mm). Two of the cases had relative afferent pupillary defect (RAPD) and early signs of compressive optic neuropathy. Four of them had limitation of ocular movements and had complaint of diplopia on up-gaze. The involvement was bilateral in 6 patients whose right eye was considered in data analysis.

Dermis

The lower eyelid dermis appeared as an echo-dense linear structure at the methyl cellulose−eyelid interface in both groups. The skin in the lower eyelid is composed of three layers: epidermis, dermis, and subdermis fat that could be seen as, hyper-echo, hypo-echo, and hyper-echo, respectively. Two patients had very thick subdermis fat pads (1.7 mm compared to normal range; 0.7−1.1 mm) that appeared as a thick hyper-echo band. These two patients had severe fat fibrosis and gaze limitation and diplopia. This finding was not consistent in other chronic TAO patients, and the thickness of subdermis fat was not different significantly compared to the control group (Fig. 1). Additionally, in the aspect of dermis and orbicularis muscle characteristics, there was no significant difference between the two groups ($P = 0.23$).

Orbital septum

Orbital septum could be seen as a highly echo-dense structure (Fig. 2A) lying just beneath the hypo-echo tissue of orbicularis muscle. Orbital septum was appreciated as a separate echo-dense layer in normal group. In Chronic TAO patients, it was seen very easily and with a very bright echo-density (Fig. 2B). Orbital septum showed a statistically insignificant thickening compared to normal patients ($P = 0.27$), but the shape of the septum was altered because of change in fat bulging in chronic TAO patients in observation.

Orbital fat

The orbital fat pad, located just posterior to the orbital septum, has two components based on distinct motion characteristics and echogenisity[6] (Fig. 3). The superficial component is echo-dense and closer to the globe, while a deeper postero-inferior compartment is near the orbital floor and is relatively echo-lucent. The fat compartments have additional movement characteristics that were described in our previous study[6] with the terms “sliding” and “jelly-like or swirling”. Pattern of fat motion was revealed to be different in chronic TAO patients. Patients with chronic TAO had blocky movement compared to compartmentalized fat movements that existed in normal cases. On the other hand, most of the patients with chronic TAO lost jelly-like movement that occurred within each fat compartment in normal cases. Tracking of the fat movement also showed that range of motion of fat compartment is less in chronic TAO cases than normal subjects (Fig. 4). The analysis of superficial fat pocket motion in the maximum vertical eye excursion was 6.7 ± 0.7 mm in the normal group and 5.8 ± 0.4 in the chronic TAO group ($P < 0.001$). In comparison, the deep fat pad range of motion was lower in both groups, and the difference between the two groups was significant (2.6 ± 0.2 mm in the chronic TAO group vs 2.75 ± 0.7 mm in the normal group, $P < 0.001$).

It seemed that correlation of the limitation of fat motion with proptosis was bolder than its correlation with lower lid retraction. There was a negative correlation between the amount of lower lid retraction and fat pocket range of motion in superficial pocket (Pearson correlation coefficient = −0.77, $P < 0.001$), and the higher the retraction was, the amount of superficial fat movement decreased. This trend was found in the deep fat pad motion but was not statistically significant (Pearson correlation coefficient = −0.43, $P = 0.10$).

Proptosis and superficial fat pocket range of motion had significant negative correlation (Pearson correlation coefficient = −0.929, $P < 0.001$). Also, the amount of proptosis and deep fat pocket range of motion were significantly correlated in a negative manner (Pearson correlation coefficient = −0.53, $P = 0.04$).

In the qualitative observation of ultrasound movies of chronic TAO patients, 5 types of hyper-echogenic lesions were revealed in lower lid orbital fat pads: echo-dense points, fine bands, thick bands, cords, and total fibrosis of lower lid fat pads (Fig. 5). It was observed that these echo-dense lesions start adjacent to the orbital septum and just beneath it.

It was observed that patients with echo-dense points did not have jelly movements. On the other hand, in patients with bands, compartmentalized motion had changed toward the blocky movements. At the same time, gaze limitation and diplopia were present in the patients with tight bands, cords, and total fibrosis in the ultrasound (Table 1). All the patients that had hyper-echo cords had proptosis larger than 3 mm and larger amount of lower lid retraction, and these ultrasonic findings were more observed in lower range of motion of the fat components.

Retractor muscle

Mean length of the retractor muscle was 4.1 ± 0.9 mm in chronic TAO group whereas it was 5.7 ± 0.5 mm in the normal group ($P < 0.001$). For evaluation of retractor muscle movement, we marked one point on the lower lid retractor muscle and followed it when globe moves from lowest down-gaze to highest up-gaze. The retractor muscle range of motion

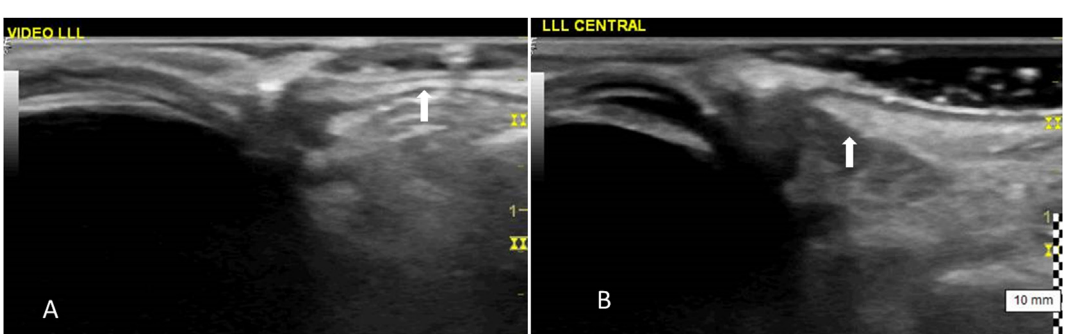

Fig. 1. A, Ultrasound of a normal lower eyelid with normal subdermis fat (arrow). B, Subdermis fat thickening (arrow) in a patient with severe chronic thyroid associated ophthalmopathy (TAO) (LLL: left lower lid).

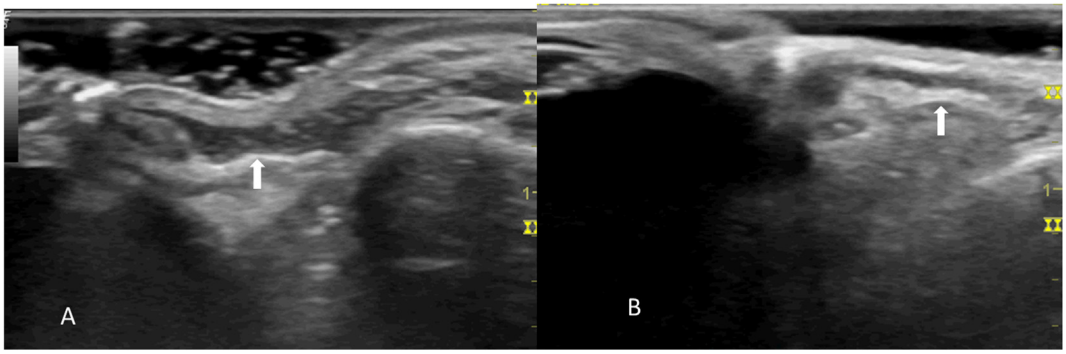

Fig. 2. A, Ultrasound image showing orbital septum in a 29-year-old man (arrow). Note the echodensity of the septum. B, Ultrasound of a 52-year-old patient with mild chronic thyroid associated ophthalmopathy (TAO) showing that echodensity of the septum (arrow) has been increased instead of decrease in older age.

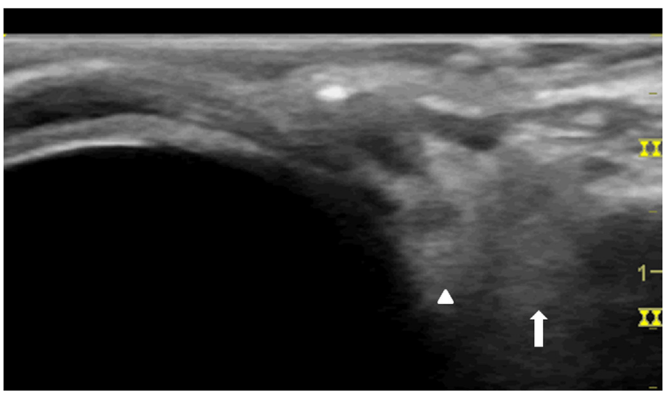

Fig. 3. Ultrasound of a normal subject showing lower lid fat compartments, arrowhead showing anterior and arrow showing inferior compartment. Note the mild difference in echodensity of the 2 compartments.

compared in the two groups in dynamic videos differed significantly between the two groups ($P < 0.001$) and was lower in the chronic TAO group, 4.34 ± 0.78 mm on average, compared to 5.41 ± 0.68 mm in the normal group (Fig. 6).

A negative correlation was found between the amount of retraction and the length of the lower eyelid retractor muscle in chronic TAO cases (Pearson correlation coefficient = −0.80, $P < 0.001$). The correlation of lower lid retraction and range of motion of the retractor muscle followed a negative trend, but it was not statistically significant (Pearson correlation coefficient = −0.35, $P = 0.19$).

There was a positive correlation between the amount of proptosis and lower lid retraction in chronic TAO cases (Pearson correlation coefficient = 0.82, $P < 0.001$).

Retractor bands

In an observational study, in comparison between normal and chronic TAO patients that have lower lid retraction less than 2 mm, without any gaze limitation, chronic TAO patients had some restriction in stretching of retractor muscle in up-gaze, whereas in normal subjects, the retractor muscle fully stretched in up-gaze. In some of these patients, some echo-dense bands were detected in ultrasound study that prevented from full stretching of the retractor muscle (Fig. 7). In cases with more significant motion limitation and more severe proptosis and retraction, there was some hyper-echo cords within the fat compartment that altered the fat motion behavior, both the movement of the fat pocket with the globe excursion and also the internal motion of fat components. These findings lead to the proposal of a new type of classification bases on observational findings in ultrasonography of lower lid in cases of chronic TAO (Table 1).

Discussion

This study revealed for the first time that the degree of fibrotic changes of lower lid fat pads correlate with the severity of clinical manifestations in chronic TAO. Current findings provide a novel view for assessing the clinicopathological soft tissue changes in chronic TAO. A new classification for observed fibrotic changes in the fat pads of the lower lid in chronic TAO is also proposed.

Many of the clinical signs and symptoms of chronic TAO can be explained by an increase in the volume of orbital tissues as it can be measured by computed tomography scans. The overall increase of orbital volume may result both from an accumulation of hydrated hyaluronan in the orbital muscles and connective tissues and an expansion of the adipose tissues within the orbit.[7]

Characteristics of the orbital adipose tissue and alterations in periorbital fat pads in chronic TAO have been the subject of interest in recent years.[7,8] Adipocytic differentiation of pre-adipocyte fibroblasts, isolated from the stromal vascular beds, gives birth to the orbital fat tissue.[9] These cells are capable of undergoing adipocytic differentiation when cultured in an appropriate medium in vitro studies.[10]

Our study conversely showed a significantly fibrotic changes in adipose tissue of patients with chronic TAO especially when it progresses to more severe stages. This finding could be related to the fibrotic process of the disease that may occur as a de novo phenomenon during the second stage of the disease or due to possibility of reverse differentiation of adipose tissue components to fibroblasts. One of the important findings of our study was that the fibrotic changes start from the tissue around the orbital septum in nearly all of the chronic

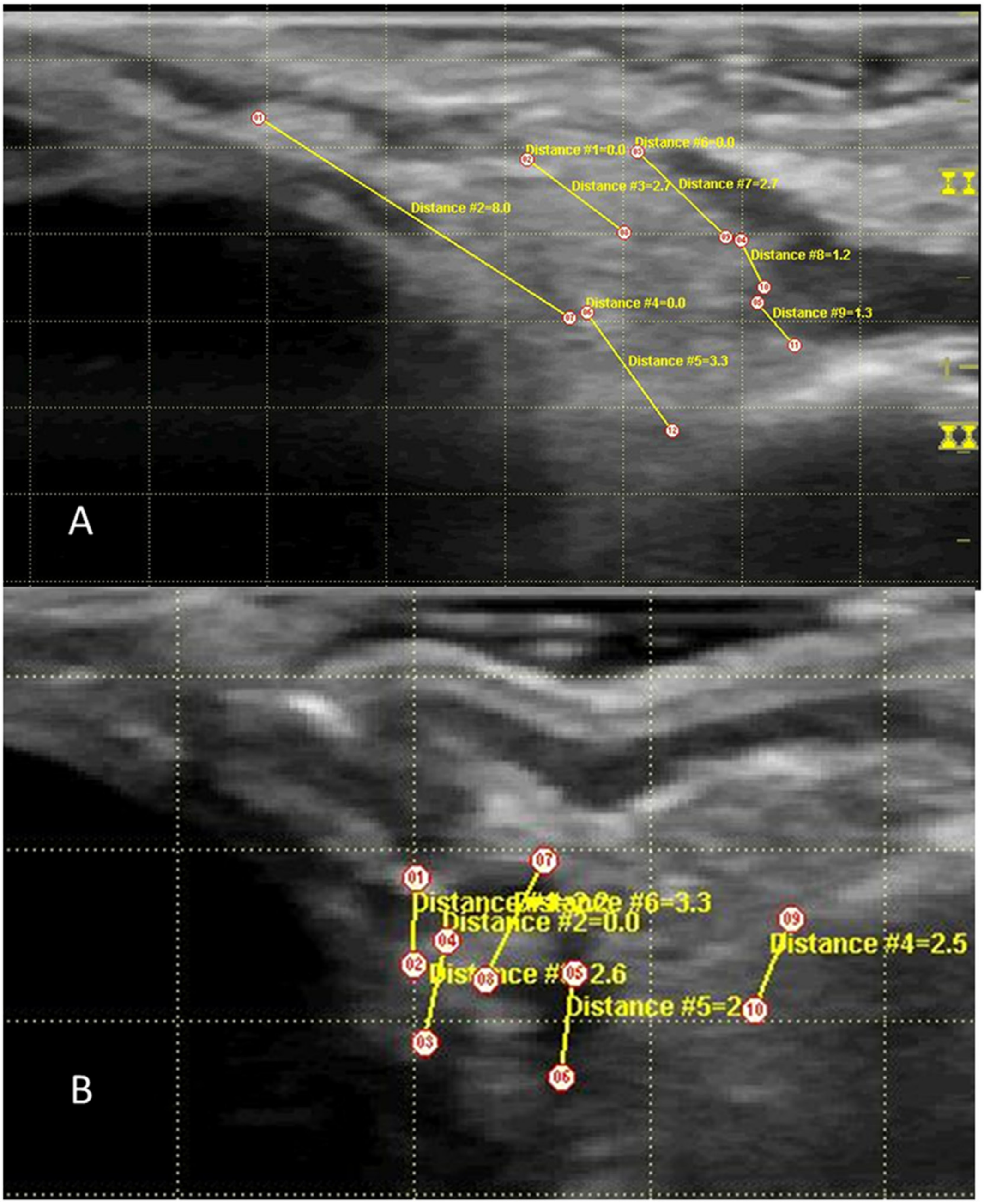

Fig. 4. Range of motion of fat compartment in 2 chronic thyroid associated ophthalmopathy (TAO) patients. A, A patient with mild lower lid involvement so that range of motion has not been restricted. B, Another patient with severe chronic TAO and restricted and blocky movement. Numerical data showing range of motion of fat compartments.

TAO patients. Then the fibrosis spreads to the fat pads located approximate to the septum. This phenomenon is comparable to the fibrotic process observed in lower lid blepharoplasty that occurs when the orbital septum has been violated. Observation of such findings suggest that some fibroblastic precursors are hosted within or around the orbital septum that activate in various occasions such as following surgical trauma or micro traumatic or inflammatory changes of the adjacent tissue that may ignite the process of differentiation of these cells toward the fibrotic tissue.

Ultrasonographic diagnostic criteria of chronic TAO is based on the following points: no mass lesion, enlarged orbital soft tissue structures with a heterogenous reflectivity, thickening of the bellies of at least two extraocular muscles, enlarged subarachnoid space of the optic nerve in case of compressive optic neuropathy, and thickened periorbital tissue. The internal reflectivity of extraocular muscles is low in patients with active disease due to edematous inflammatory infiltration and irregularly high in fibrotic end stage disease.[11,12]

The main advantages of orbital ultrasound are its low cost and availability and the lack of ionizing radiation, with a relatively short examination time ($\approx$15 min) to monitor anterior/mid-orbital soft tissues for diagnostic purposes or may

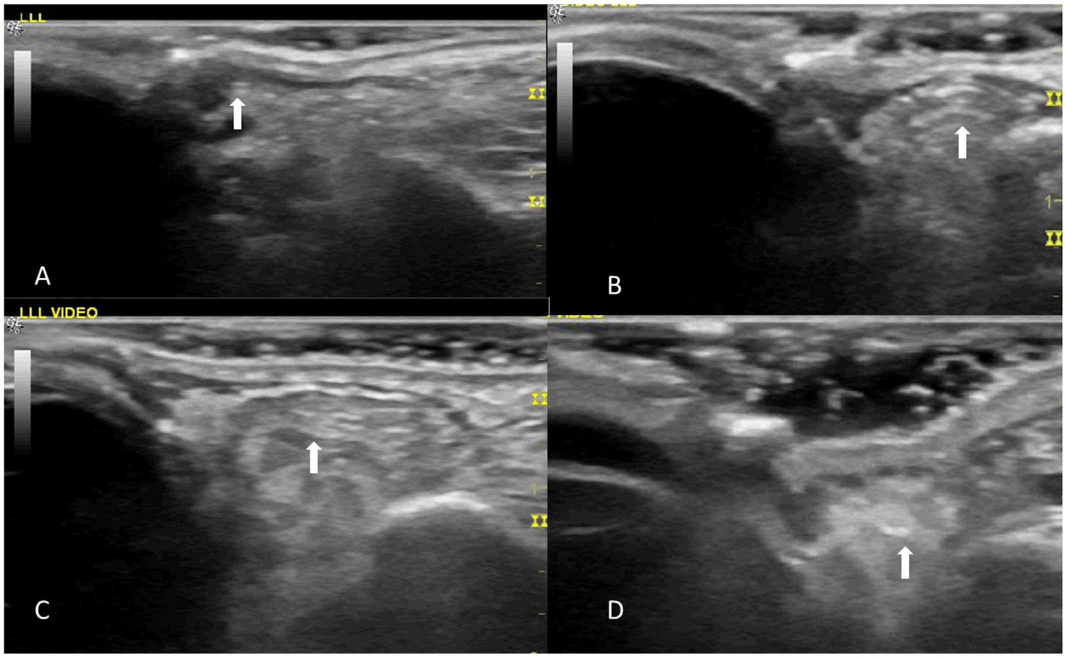

Fig. 5. Echodense lesion in the lower lid fat pad of patient with chronic thyroid associated ophthalmopathy (TAO). A, Ultrasound of a patient with mild chronic TAO and without any clinical finding except proptosis (3 mm) and mild retraction (1 mm) on clinical evaluation. Note the echodense point lesions just beneath the septum (arrow). B, Ultrasound showing some fine band (arrow) just beneath the septum. Ultrasound captured movie of this patient had blocky movement compared to compartmentalized normal movement. C, Ultrasound of lower eyelid of a patient with lower lid retraction and mild diplopia showing multiple bands (arrows). D, Lower lid fat fibrosis (arrow) in a patient with restricted eye movement and severe diplopia. (LLL: left lower lid).

Table 1
Staging of densities visible with ultrasound and its associated clinical findings.

	Types of ultrasound finding lesions	Effect on fat motion
Stage 1	Echodense points	Loss of jelly movements
Stage 2	Fine bands	Decrease in compartmentalized movement
Stage 3	Thick bands	Blocky movement, lower lid retraction
Stage 4	Cord and total fibrosis	Gaze limitation and strabismus disorders

be to assess the therapeutic response in experienced hands. The main drawback of this technique is its high intra- and inter-observer variability concerning accurate performance.

In our study, we found that occurrence of fat fibrosis that can be seen as various types of hyper-echogenic lesions, and limitation of motion in fat pockets in dynamic analysis was correlated with higher proptosis and larger amount of lower lid retraction. Jelly-like motion[6] of fat components was diminished as these hyper-echo particles were nearly immobile and were not fully attached to each other. Occurrence of point fibrosis may cause some bridge formation between these fat particles, so that they lost motion in their lobule or compartments. When these fibrotic lesions had grown larger, the field of involved area increases in size, so that these fibrotic bands may cause bridge formation between fat compartments, and finally lead to a blocky movement within the fat tissue.

On the other hand, depending on the location and severity of these lesions, multiple clinical effects may develop. Although at the stage of point fibrotic lesions, any relevant clinical impact is not demonstrable, or very small if any, in the next stage, when band lesions appeared, lower lid retraction, strabismus disorders, and diplopia emerged. We think that these fibrotic bands retracted the lower lid by making small but multiple bridges between the fat tissues. The fat range of motion and range of motion of the retractor muscle was also diminished in this stage. It should be investigated if the strabismus and diplopia in this group is correlated to a similar fibrotic process that might occur in the extraocular muscles. In the current study, 4 patients had very severe fibrosis in the lower eyelid, which not only had diplopia but also tight globe and restricted ocular movements. Two of them had RAPD, and compressive optic neuropathy was present and underwent orbital decompression. As mentioned, it is difficult to correlate such findings of fibrotic bands to the clinical problems of the patients, but it is reasonable to consider development of similar process in the extraocular muscles that prevents the relaxation of the muscles and decrease its range of motion.

Range of motion of the retractor muscle was diminished in the current study, and this diminution correlated with the higher amounts of retraction and proptosis; also in the observational study, in severe fibrotic patients, this amount of limitation was significant when comparing range of motion of retractor muscle in chronic TAO patients and normal cases. Usually lower lid follows the globe movement when globe comes from down-gaze to up-gaze; however, in chronic TAO patients, this association would be decreased so that when the globe goes up, the lower lid cannot follow it to the extent present in a normal individual, so that the amount of scleral show would be more than normal controls that is named lower lid lag. Here, we found some fibrotic bands that might have a restrictive effect on full

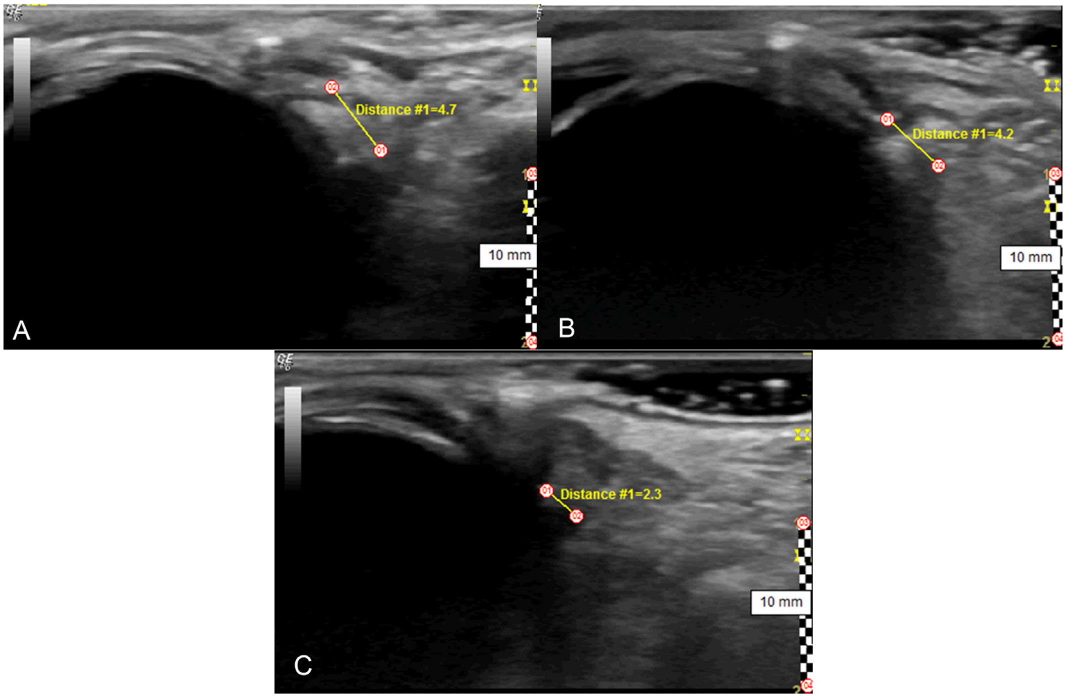

Fig. 6. Range of motion of retractor muscle. A, In a normal subject. B, In a patient with lower lid retraction. C, Restricted motion in a patient with severe chronic thyroid associated ophthalmopathy (TAO). Numerical data showing range of motion of retractor muscle.

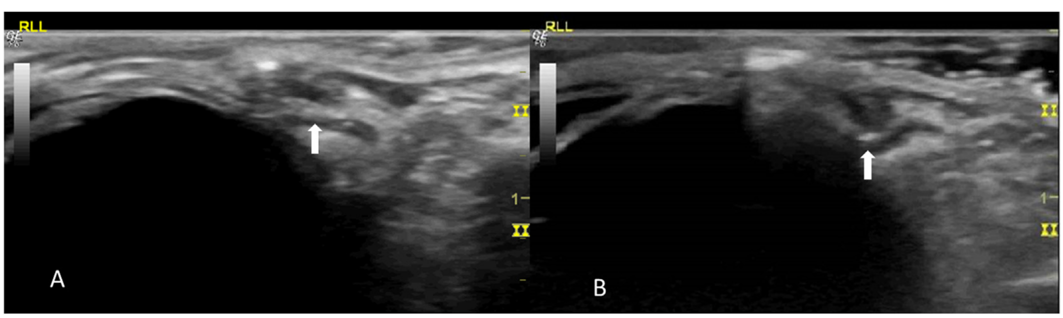

Fig. 7. A, Ultrasound of a normal subject in up-gaze showing that lower lid retractor muscle has been fully stretched (arrow). B, Ultrasound of a patient with lower lid retraction in up-gaze shows that lower lid retractor cannot be stretched (arrow).

stretching of the lower lid or followability of the lower lid after the globe. Although in the active phase of the disease, overactivity of the sympathetic system has been proposed as one of the causes of upper and lower lid retraction, when chronicity of the disease occurs, fibrous formation within the retractor muscle and fibrotic bands from lower lid fat pads to the retractor muscle may also aggravate the problem.

Although MRI and CT scans are the most useful methods for imaging in chronic TAO patients, they cannot demonstrate lower lid compartments as the ultrasound does dynamically. Ultrasound enabled us to image the lower lid retractor muscle and lower lid fat pad pathologies with fine details, besides allowing the detection of anatomical, structural, and mechanical abnormalities. Motion analysis and its repeatability for many times, and evaluation of the coincident movement of the adjacent structures in lower lid is more easy by means of ultrasound. Also, lack of ionizing radiation in the head and neck area, that is a risk factor for thyroid carcinoma, is the advantage of the ultrasound that might be substituted with some of the sessions of CT-scan if it can be utilized as a means of follow-up.

Despite satisfactory and reliable lower lid evaluation in chronic TAO patients using ultrasound, we cannot ignore some limitation in our study. First, the small sample size could have an adverse impact on the statistical analysis and conclusion. The second disadvantage is high intra- and inter-observer variability of ultrasound findings concerning accurate measurements. This is a basic source of error in the ultrasound technique that is a user-dependent modality and needs training and experience. Third, we know the findings of this study may not be consistent in all TAO patients, and a study with all possible clinical forms of the TAO in both active and inactive phases should be performed to compare the findings in active and chronic TAO patients.

In conclusion, this study provides for the first time the dynamic explanation for pathological changes in lower lid compartments in chronic TAO. Although it may not be consistent in all of the patients with chronic TAO, taking into consideration all of the findings in ultrasonic evaluation of chronic TAO patients beside clinical and functional examination would help the clinician to consider a better approach. We propose that appearance of these changes underlies and precedes the severe clinical findings. Although usually chronic TAO patients have passed an active phase before going toward fibrotic or inactive phase, some patients with chronic TAO have only fibrotic phase whose diagnosis with non-invasive and low cost imaging modalities such as ultrasound may help them to be managed better and prevent them from developing a frozen blind eye. Finally, it is theoretically acceptable that the best time for prevention of orbital stigmata in chronic TAO may be in point fibrosis stage, but it needs to be investigated in a new study. Future studies could aim to answer whether or not ceasing the point lesions from changing into bands, and then from bands to cords could prevent the clinical problems of this group of patients.

References

1. Prabhakar BS, Bahn RS, Smith TJ. Current perspective on the pathogenesis of Graves' disease and ophthalmopathy. *Endocr Rev*. 2003;24(6):802–835.
2. Jankauskienė J, Imbrasienė D. Investigations of ocular changes, extraocular muscle thickness and eye movements in Graves' ophthalmopathy. *Med Kaunas*. 2006;42(11):900–903.
3. Regensburg NI, Wiersinga WM, Berendschot TT, Potgieser P, Mourits MP. Do subtypes of graves' orbitopathy exist? *Ophthalmology*. 2011;118(1):191–196 [Epub 2010 Jul 29].
4. Yamamoto K, Itoh K, Yoshida S, et al. A quantitative analysis of orbital soft tissue in Graves' disease based on B-mode ultrasonography. *Endocrinol Jpn*. 1979;26(2):255–261.
5. Rajabi MT, Jafari H, Mazloumi M, et al. Lower lid retraction in thyroid orbitopathy: lamellar shortening or proptosis? *Int Ophthalmol*. 2014;34(4):801–804.
6. Rajabi MT, Papageorgiou K, Chang SH, et al. Ultrasonographic visualization of lower eyelid structures and dynamic motion analysis. *Int J Ophthalmol*. 2013;6(5):592–595.
7. Valysasevi RW, Harteneck D, Dutton DM, Bahn RS. Stimulation of adipogenesis, peroxisome proliferator-activated receptor[gamma] (PPAR [gamma]), and thyrotropin receptor by PPAR[gamma] agonist in human orbital preadipocyte fibroblasts. *J Clin Endocrinol Metab*. 2002;87(5):2352–2358.
8. Wu SL, Yang CSJ, Wang HJ, Liao CL, Chang TJ, Chang TC. Demonstration of thyrotropin receptor mRNA in orbital fat and eye muscle tissues from patients with Graves' ophthalmopathy by in situ hybridization. *J Endocrinol Invest*. 1999;22(4):289–295.
9. Chen X, Hausman DB, Dean RG, Hausman GJ. Differentiation-dependent expression of obese (ob) gene by preadipocytes and adipocytes in primary cultures of porcine stromalvascular cells. *Biochim Biophys Acta*. 1997;1359(2):136–142.
10. Tontonoz P, Hu E, Spielgeman BM. Stimulation of adipogenesis in fibroblasts by PPAR gamma 2, a lipid-activated transcription factor. *Cell*. 1994;79(7):1147–1156.
11. Ossoinig KC. The role of standardized echography in Graves' disease. *Acta Ophthalmol Suppl*. 1992;204:81.
12. Prummel MF, Suttorp-Schulten MS, Wiersinga WM, Verbeek AM, Mourits MP, Koornneef L. A new ultrasonographic method to detect disease activity and predict response to immunosuppressive treatment in Graves' ophthalmopathy. *Ophthalmology*. 1993;100(4):556–561.