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Thyroid-associated Orbitopathy: Quantitative Evaluation of the Orbital Fat Volume and Edema Using IDEAL-FSE

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ABSTRACT

Background and Purpose: To compare orbital quantitative data obtained by fast spin-echo iterative decomposition of water and fat with echo asymmetry and least-squares estimation (FSE-IDEAL) in patients with thyroid-associated orbitopathy (TAO) and healthy controls and to investigate the characteristics of these data in TAO patients.
Materials and Methods: Twenty-two TAO patients (4 males and 18 females; median age 51.0 years) and 22 healthy subjects (5 males and 17 females; median age 50.5 years) underwent orbital T2-weighted FSE-IDEAL. The water fraction in orbital fat was defined as the signal intensity (SI) *water* / (SI *water* + SI *fat*). The orbital fat volume was measured on fat images. The degree of proptosis was evaluated using in-phase imaging. Mann–Whitney U test was used to compare these quantitative data in the two groups. In TAO patients we ascertained the correlation among these values with the Spearman's rank correlation coefficient.
Results: In TAO patients, the water fraction (right and left, $p = 0.04$), fat volume (right and left, $p = 0.03$) and degree of proptosis (right and left, $p < 0.01$) were higher than in the controls. In TAO patients, only the water fraction and the fat volume of left orbit showed negative correlation ($p = 0.01$).
Conclusion: The water fraction of orbital fat, the orbital fat volume and the degree of proptosis obtained with FSE-IDEAL were higher in TAO patients than in the controls. The water fraction was a new parameter for differentiating between TAO patients and healthy subjects.

1. Introduction

Thyroid-associated orbitopathy (TAO) is characterized by proptosis due to an increase in the orbital fat- and extraocular muscle volume [1]. In patients with TAO, the T2 value of extraocular muscles is prolonged [2,3] and the water fraction in orbital fat is increased [4]. As variations in orbital structures and the presence of euthyroid TAO make it difficult to distinguish between TAO patients and healthy subjects, objective methods are needed for their differentiation.

Computed tomography (CT) has been used to assess the extraocular muscle- and orbital fat volume in patients with TAO [3,5,7]. However, the low soft-tissue contrast on CT images makes it difficult to separate out orbital fat and ocular radiation exposure limits its clinical use. As magnetic resonance imaging (MRI) without ionizing radiation yields orbital images with excellent soft-tissue contrast in any plane, it has been used for evaluating TAO [8–11]. To compare orbital structures in TAO patients and controls, a computer-assisted method for the global and regional segmentation of orbital fat on T1- and T2-weighted images

Abbreviations: CAS, clinical activity score; FSE-IDEAL, fast spin-echo iterative decomposition of water and fat with echo asymmetry and least-squares estimation; IQR, interquartile range; SD, standard deviation; SI, signal intensity; TAO, thyroid-associated orbitopathy

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Fig. 1. Control Axial water- (A) and fat image (B). Yellow circles identify the ROIs. Using the average signal intensity (SI) in the ROIs, the water fraction in orbital fat was calculated as SI water / (SI water + SI fat).

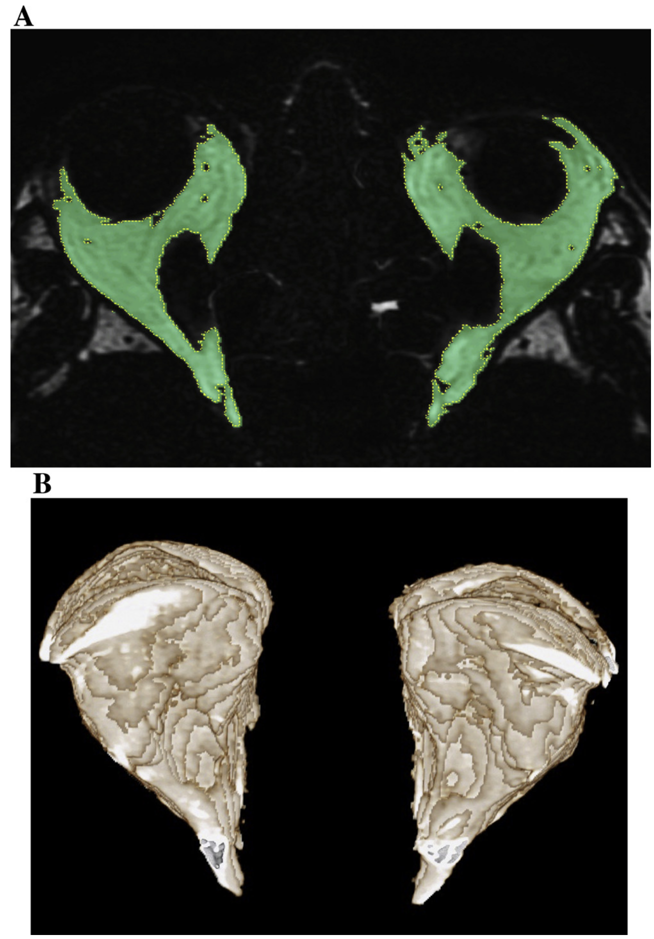

Fig. 2. Control Axial fat image (A). The selected orbital fat is green. We separated fat tissue using an adequate signal intensity (SI) threshold and manually removed extraorbital fat. The average SI in the internal rectus muscle was 92; the standard deviation (SD) was 39. In orbital fat, the the average SI was 1306 and the SD was 54. Therefore the threshold value was [(92 + 39) + (1306 - 54)] / 2 = 691. Using FSE-IDEAL images we then produced 3D reconstruction images of the bilateral orbital fat (B) and measured the orbital fat volume on a workstation.

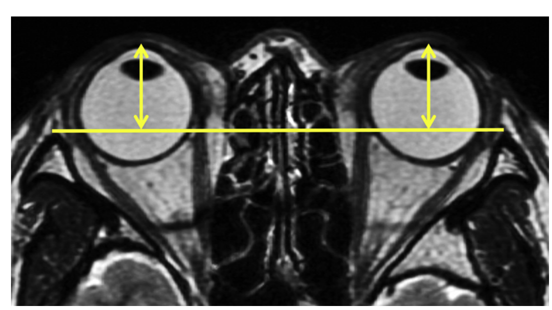

Fig. 3. Control Maximum-diameter slice in-phase image. The yellow horizontal line connects the bilateral frontal processes in the zygomatic bones. The distance from the top of the cornea to the horizontal line was measured to determine the degree of proptosis.

(WI) [12], T2-WI and dynamic contrast-enhanced MRI [13], T1-WI [8], and comparison of the T2 relaxation time [10] have been used.

Fast spin-echo iterative decomposition of water and fat with echo asymmetry and least-squares estimation (FSE-IDEAL), a novel 3-point DIXON method, can be used to estimate the water fraction in- and the volume of orbital fat [4,14,15]. It facilitates the quantitative evaluation of orbital fat, the monitoring of the patient response to therapy, and the prediction of the response to methylprednisolone-pulse therapy [4]. However, no studies have employed FSE-IDEAL to compare the orbital structures in TAO patients and healthy subjects.

We hypothesized that pathological changes in the orbital fat of TAO patients may result in an increase in the water fraction in orbital fat and its volume and may exacerbate proptosis and that such findings may help to differentiate TAO patients from healthy subjects. We compared orbital quantitative data obtained by FSE-IDEAL in TAO patients and normal controls and examined potential correlations in data from TAO patients.

2. Materials and Methods

2.1. Subjects

Our prospective study was approved by ———————— the institutional review board. Informed consent was obtained from all participants before entry into the study.

We recruited 22 patients (4 males, 18 females; mean age 51.0 years; range, 30 - 82 years) who received a clinical diagnosis of TAO between December 2013 and April 2016. The diagnosis was based on their clinical activity score (CAS), including pain, eyelid erythema or edema, conjunctival hyperemia and chemosis, and caruncle swelling [16]. The median interval between TAO onset and diagnosis was 3.5 months (range 1 - 60 months); the mean CAS was 1.59 ± 1.00 (range 1 - 4). All patients underwent orbital FSE-IDEAL imaging to evaluate the water fraction in orbital fat, the orbital fat volume, and the degree of proptosis.

We also recruited 22 healthy volunteers (5 males and 17 females, mean age 50.5 years, range 29 - 70 years) for orbital FSE-IDEAL imaging.

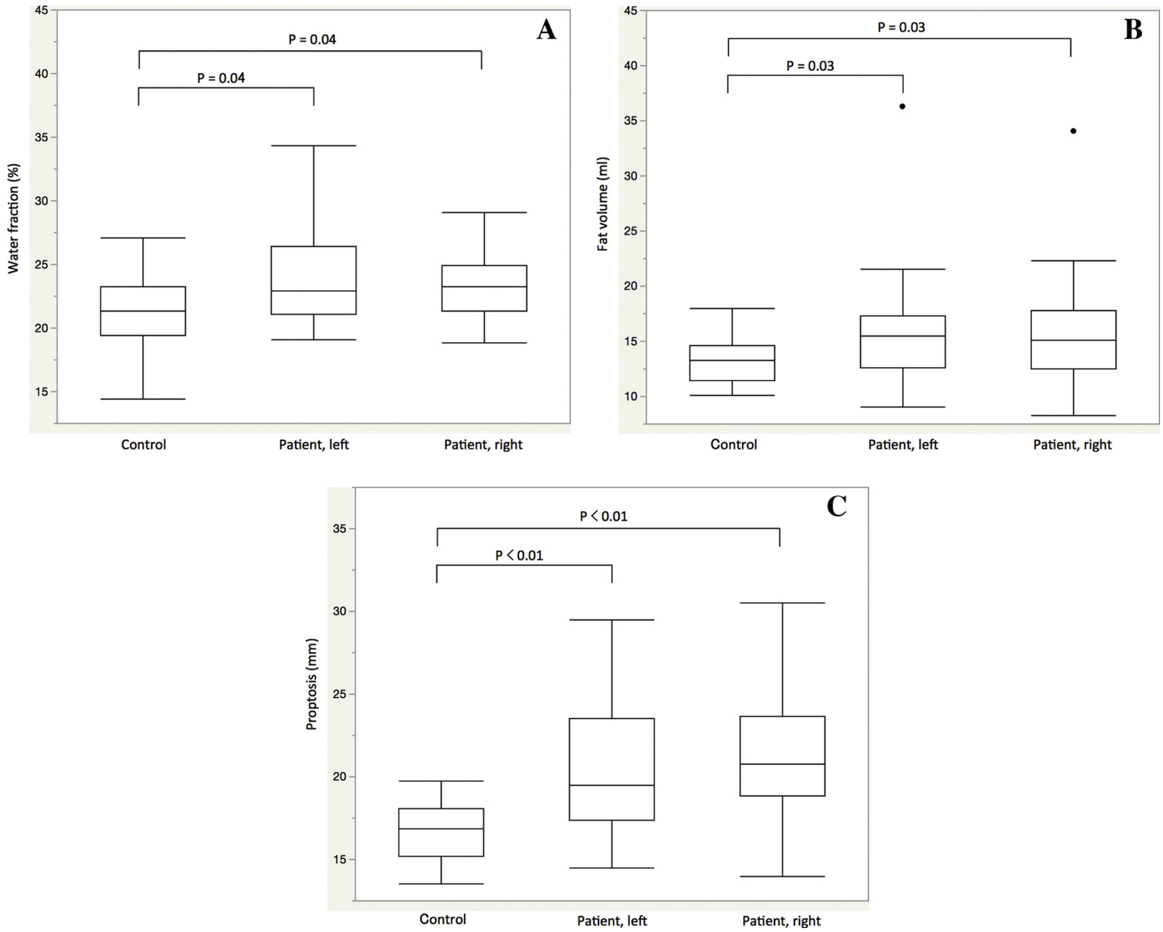

Fig. 4. Comparison of the quantitative data of 22 TAO patients and 22 healthy controls by Mann–Whitney U test.
Box-and-whisker plots show water fraction of orbital fat (A), orbital fat volume (B) and proptosis (C). The plots show the minimum and maximum values (lower and upper horizontal lines, respectively), the median values (line in box) and the interquartile ranges (box) in each dataset. Significant differences are indicated with the P value. In TAO patients, the value of water fraction, fat volume and degree of proptosis were significantly higher than in the controls.

2.2. MRI

All images were acquired on a 3 T scanner (Signa Excite HD 3.0; GE Medical Systems, Milwaukee, WI, USA; gradient strength, 40 m T/m; slew rate, 150 T/m/s) using an 8-channel phased-array brain coil. We optimized the T2-weighted FSE-IDEAL sequence (repetition time/echo time, 6000/100 ms; flip angle, 90°; image matrix, 288 × 160; field of view, 160 x 160 mm; slice thickness/gap, 2/0 mm; asymmetric echo shifts, -π/6, π/2, 7π/6; number of acquisitions, 3; number of slices, 32; scan time, 2 min 42 sec) and obtained orbital water- and fat images and in-phase images for all subjects.

2.3. Orbital fat water fraction-, orbital fat volume-, and proptosis measurements

Two radiologists (with 10 and 13 years' experience) reviewed and analyzed image data independently, and the average values of the 2 readers were collected as the final results. A region of interest (ROI) was placed in the orbital fat on FSE-IDEAL images of water and fat and the average signal intensity (SI) in the ROIs was measured. The water fraction was defined as SI water / (SI water + SI fat) to assess orbital fat edema (Fig. 1) on the basis of fat fraction [SI fat / (SI water + SI fat)] [14].

The orbital fat volume in both eyes was measured on a workstation (AZE Virtual Place Raijin; AZE Ltd., Tokyo, Japan). Fat tissue was separated from other structures using the threshold value recorded as the mean value between the average SI plus the standard deviation (SD) of the ROI in the internal rectus muscle and the average SI minus the SD of the ROI in orbital fat; dispersions in the SI of the ROIs were taken into account [4]. The fatty marrow of orbital bone and outer fat were removed manually and the orbital fat volume was automatically measured on the workstation (Fig. 2).

To evaluate proptosis, maximum-diameter slice in-phase images were selected and the perpendicular distance from the top of the cornea to a line connected to the bilateral frontal processes of the zygomatic bones was recorded [8] (Fig. 3).

2.4. Statistical analysis

All statistical analyses were performed with JMP Pro version 14.0.0 (SAS Institute Inc., Cary, NC, USA) and MedCalc software version 15.8. × 86 (bvba, Ostend, Belgium).

Interobserver variability was determined by Bland-Altman analysis. Mann–Whitney U test was performed to compare quantitative data obtained with IDEAL (water fraction of orbital fat, orbital fat volume, proptosis) between healthy volunteers and TAO patients. For TAO patients, we ascertained the correlation among quantitative IDEAL data, between quantitative data and age, the duration of TAO, or the CAS with the Spearman's rank correlation coefficient.

The bilateral orbits were examined separately because unilateral TAO results in excess fat exophthalmos on the affected side [6]. Differences of $p < 0.05$ were considered statistically significant.

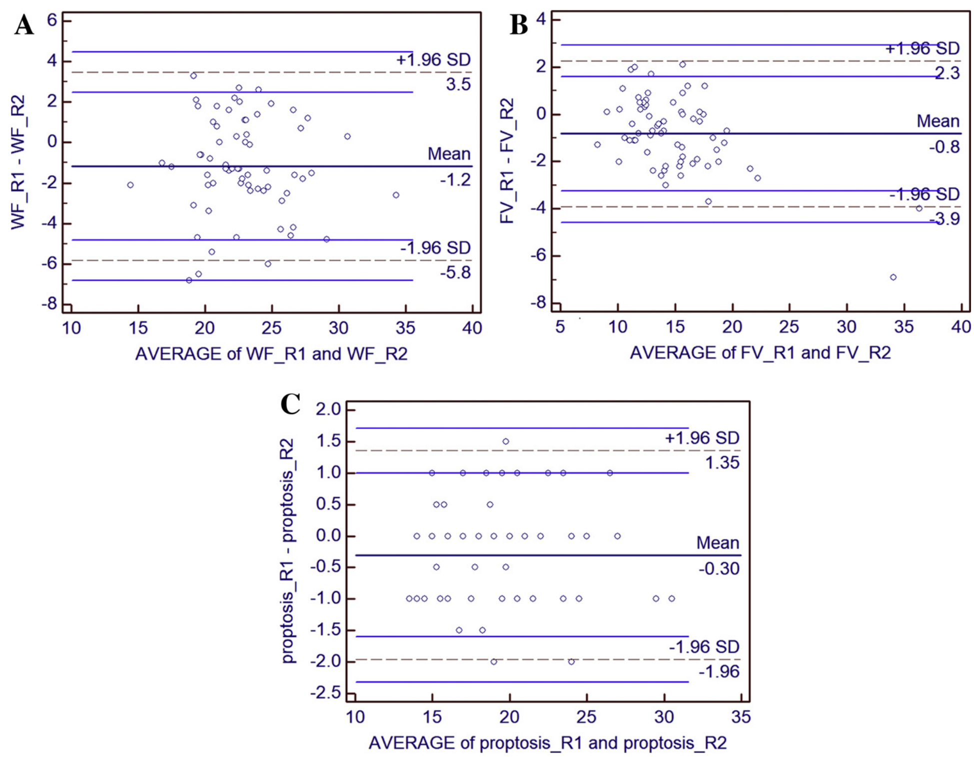

Fig. 5. Bland-Altman analysis confirming the interobserver variability or the water fraction (WF) (A), the volume of orbital fat (FV) (B) and the proptosis (C) on FSE-IDEAL images of the participants. R1 = reader1, R2 = reader2.

Table 1
Correlations among data obtained in 22 TAO patients.

		Water fraction		Fat volume		Proptosis	
Right		*r* value	*P* value	*r* value	*P* value	*r* value	*P* value
	Proptosis	−0.10	0.67	0.35	0.11	-	-
	Water fraction	-	-	−0.35	0.11	-	-
	Age	0.04	0.86	−0.01	0.98	−0.07	0.76
	TAO duration	−0.36	0.10	−0.12	0.59	0.04	0.84
	CAS	−0.17	0.44	0.16	0.47	0.30	0.18
Left		Water fraction		Fat volume		Proptosis	
		r value	*P* value	*r* value	*P* value	*r* value	*P* value
	Proptosis	−0.15	0.51	0.32	0.15	-	-
	Water fraction	-	-	−0.53	0.01	-	-
	Age	0.39	0.07	0.01	0.96	−0.01	0.97
	TAO duration	0.15	0.51	−0.15	0.50	0.06	0.80
	CAS	0.04	0.84	0.16	0.47	0.20	0.36

TAO: thyroid-associated orbitopathy, CAS: clinical activity score

3. Results

There was no significant difference in the age of our TAO patients and controls (p = 0.50) and in their gender (p = 0.71).

As shown in Fig.4, comparison between TAO patients and the controls showed that the water fraction in bilateral orbital fat was significantly higher in TAO patients; their fat volume was significantly greater only in the left orbit. The degree of proptosis was also significantly higher in TAO patients. Bland-Altman analysis showed that low interobserver variability for all measurements (Fig.5).

In TAO patients, there was no significant correlation between the water fraction and the orbital fat volume, proptosis, the age, disease duration, or the CAS, between the orbital fat volume and the age, the TAO duration, or the CAS, nor was there a significant correlation between proptosis and the age, disease duration, or the CAS. However, there was a significant negative correlation between water fraction and fat volume in the left orbit (r = -0.53, p = 0.01). The values in right orbit showed a tendency to correlate negatively though there was no significant correlation (r = -0.35, p = 0.11) (Table 1).

4. Discussion

To the best of our knowledge, this is the first quantitative evaluation of TAO using FSE-IDEAL imaging. We document a significant difference between TAO patients and the controls with respect to the water fraction in orbital fat, the orbital fat volume and the degree of proptosis. In TAO patients we found a negative correlation between water fraction and fat volume in the left orbit but detected no significant correlation between them in the right orbit.

The water fraction in orbital fat was greater in TAO patients than in the controls. Previous histological studies revealed lymphocytic infiltration and edema due to the accumulation of hydrophilic, interstitial glycosaminoglycans in the orbital fat and extraocular muscles of TAO patients [17,18]. Water retention was closely related to high osmolarity due to the accumulation of mucopolysaccharides in the orbit [19] and swollen orbital tissues impede venous outflow from the orbit.

As we found that the water fraction was not positively correlated with the orbital fat volume, we posit that its increase in TAO patients reflects the accumulation of mucopolysaccharides rather than congestion due to swollen orbital tissues. Although prior studies have demonstrated that the T2 signal intensity [13] and the T2 values of extraocular muscles differed significantly between TAO patients and controls [2,3,13], ours is the first study to compare the water fraction in orbital fat between TAO patients and healthy subjects. The water fraction may be of diagnostic value, especially in patients whose extraocular muscles are of normal size.

On FSE-IDEAL images, the degree of proptosis was significantly greater in our TAO patients than the controls and it was correlated with the orbital fat volume. Our findings are consistent with earlier conventional MRI- [8,12] and CT studies. Nishida et al. [21] reported that orbital fat was more closely correlated with proptosis than the status of extraocular muscles; they suggested that the increase in the orbital fat volume was larger than that of all extraocular muscles together. Their findings show that the increase in the orbital fat volume is an important contributor to proptosis.

Others reported that the orbital fat volume and proptosis were significantly correlated with the CAS [12], that prolonged TAO was associated with a higher orbital fat volume [22], and that TAO patients showed an age-related increase in the orbital fat volume [20]. We, on the other hand found no significant correlation between the quantitative values of orbital fat, i.e. its water fraction and volume, and the degree of proptosis, the patient age, the disease duration, and the CAS. In an earlier study [12], the mean CAS of TAO patients was 1.83 ± 0.81; it was 1.59 ± 1.00 in our patients. Japanese TAO patients often present with orbital inflammation despite low CAS scores [23]. In another study [22] patients whose disease duration exceeded one year were compared with patients with shorter disease duration; in our series the median TAO duration was 3.5 months.

In our patients there was a negative correlation between the water fraction and the fat volume in only left orbit, and the values in right orbit showed a tendency to correlate negatively though there was no significant correlation. We posit that the correlation reflects the prolonged TAO-related increase in the orbital fat volume and the high value of water fraction in acute phase.

Our study has some limitations. First, although we used power analysis to determine our sample size, the number of TAO patients was small, consequently, the sensitivity for detecting inter-value correlations may have been reduced. Second, it was difficult to analyze the correlation between TAO duration and other values because TAO phase of the patients was different from each other. Lastly, the correct cutoff value for the water fraction and the orbital fat volume in TAO patients and their controls remain to be determined.

5. Conclusions

The water fraction in orbital fat, orbital fat volume and the degree of proptosis determined by FSE-IDEAL were higher in our TAO patients than in the healthy controls. As the water fraction in orbital fat obtained by FSE-IDEAL is a new parameter for differentiating between TAO patients and healthy subjects, we recommend that it be added to the diagnostic criteria of TAO.

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Declarations of interest

None.

Contributors

Authors' contributions YK and KT designed the study. YK wrote the initial draft of the manuscript. YK and HT contributed to analysis and interpretation of data. KT and KA assisted in the preparation of the manuscript. All other authors have contributed to data collection and interpretation, and critically reviewed the manuscript. All authors approved the final version of the manuscript, and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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