Radiologic Parameters of Orbital Bone Remodeling in Thyroid Eye Disease

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PURPOSE. To radiologically examine for the presence of bony remodeling of the orbit in thyroid eye disease (TED).

METHODS. Computed tomography (CT) scans of 248 orbits of 124 patients with TED and 185 orbits of 138 controls were retrospectively reviewed, and the following parameters measured: the angle of the inferomedial orbital strut (AIOS), the angle of the medial wall (AMW), and the diameters of the extraocular muscles. The association of TED with the AIOS or AMW was analyzed with linear regression models, and the correlations between the AMW or AIOS measurements with the extraocular muscle measurements were determined.

RESULTS. Overall, the AIOS was found to be larger ($P < 0.001$) and the AMW smaller ($P = 0.045$) in patients with TED compared to controls. After adjusting for age and sex, the larger AIOS in TED remained significant ($P < 0.001$), but the smaller AMW in TED patients was no longer significant ($P = 0.07$). There was a negative correlation between AMW and the calculated average cross-sectional area of the medial rectus in TED ($r = -0.23, P = 0.01$).

CONCLUSIONS. A difference in the structure of the bony orbit in TED compared to controls may be demonstrated by the AIOS and AMW radiological parameters. This likely represents the presence of bony remodeling in TED, which may be related to the expansion of the intraorbital soft tissue volume.

Keywords: thyroid eye disease, bony remodeling, inferomedial orbital strut, angle of the medial wall, spontaneous decompression

Thyroid eye disease (TED) or thyroid-associated orbitopathy is an autoimmune inflammatory disorder of the orbit and periorbital tissues that most commonly occurs in patients with Graves’ disease,1,2 and less commonly in patients with Hashimoto’s thyroiditis3–5 or in patients who are euthyroid.6 The pathologic changes that occur in TED primarily affect the extraocular muscle and orbital fat compartments, both of which can increase in size.7–9 It is widely recognized that this increase in volume of the intraorbital contents within the confines of the bony orbit may lead to dysthyroid optic neuropathy (DON), increased intraocular pressures, proptosis, and venous congestion leading to chemosis and periorbital edema.10–14 However, the effect of increased intraorbital soft tissue volume and intraorbital pressure on the bony orbit itself has been sparsely studied. Thus, the aim of this study was to examine radiologic parameters that may indicate the presence of bony remodeling of the orbit in TED.

MATERIALS AND METHODS

Subjects
A total of 124 patients with TED who underwent computed tomography (CT) scans of their orbits contributed 248 orbits to this retrospective study. Diagnosis of TED was according to the Bartley and Gorman criteria15 in which TED is considered to be present if eyelid retraction occurs in association with laboratory evidence of thyroid dysfunction, proptosis, optic nerve dysfunction, or extraocular muscle involvement. If eyelid retraction is absent, then TED may be diagnosed only if exophthalmos, optic nerve involvement, or restrictive myopathy is associated with thyroid dysfunction and no other cause for the ophthalmic features is apparent. CT images were of 1-mm-thick cuts according to the Image-Guided Surgery (IGS) protocol done for preoperative planning, or of 3-mm-thick cuts when done either for diagnostic purposes or in the pre-IGS era. Where more than one CT scan was available, the latest preoperative scan was used for the study. All CT scans included for analyses had no previous orbital or sinus surgery or any other orbital pathology besides TED.

A total of 138 patients who had no known history of any thyroid disorders or orbital disease but who had CT scans of their face or orbits were also included in the study as controls. Indications for the CT scans included suspected orbital fractures, preseptal or facial cellulitis, superficial skin lumps, and evaluation of conditions affecting the nose or throat. In CT scans in which one orbit was affected by disease, only the fellow orbit was included as a control. Forty-seven patients contributed CT scans of both orbits, and 91 patients
contributed CT scans of a single normal orbit to the study; hence, 185 normal orbits were used as controls.

The study protocol was performed in accordance with the tenets of the World Medical Association’s Declaration of Helsinki, and ethics approval was obtained from the National Health Group Domain Specific Review Board.

**Radiologic Analysis**

Standard axial and direct coronal nonoverlapping contiguous CT scans of the orbits were reviewed on a digital picture archiving and communication system, Centricity Enterprise Web version 3.0 (GE Medical Systems, Waukesha, WI, USA), and angle measurements made using the angle measurement tool. In studying the bony structures of the orbit, the images were viewed at window level of 450 H and window width of 1500 W. Examination for the presence of bony remodeling (Fig. 1) was undertaken by measuring the angle of the inferomedial orbital strut (AIOS) and the angle of the medial wall (AMW).

In the coronal planes, the AIOS was defined as the angle between the medial wall and the orbital floor, centered at the orbital strut. The AIOS was measured in degrees at three points (Fig. 2): anteriorly (the first cut behind the lacrimal sac), at the middle (the halfway point between anterior and posterior), and posteriorly (the last cut near the apex where the angle between orbital floor and medial wall can be reliably measured).

In the axial plane, the AMW was studied at the midorbit where the lengths of the optic nerve, medial rectus, and lateral rectus were all simultaneously best visualized. The degree of convexity/concavity of the medial wall of the orbit was measured as follows (Fig. 3). Point 1 was defined at the nasal bone and start of the medial wall. Line A was drawn from point 1 perpendicular to the interzygomatic line. Point 2 was defined...
as the maximum excursion of the medial wall from line A. Line B was drawn joining point 1 and point 2. The AMW in degrees was defined as the angle (in red) between lines A and B. The red marking and the blue and dotted white lines were added for illustrative purposes, and were not obtained by the software used for AMW measurements.

**Statistical Analysis**

Statistical analysis was performed using IBM SPSS Statistics for Macintosh, Version 24.0 (IBM Corp., Armonk, NY, USA). Normality of data was assessed using the Shapiro-Wilk test. Statistical analysis was performed using IBM SPSS Statistics for Macintosh, Version 24.0 (IBM Corp., Armonk, NY, USA). Statistical analysis was performed using IBM SPSS Statistics for Macintosh, Version 24.0 (IBM Corp., Armonk, NY, USA).

**RESULTS**

Table 1 shows the demographics of the study participants. There were no significant differences in age, sex, or race between the TED and control groups.

As shown in Table 2, the mean AIOS (±SD) in degrees at the anterior, middle, and posterior cuts were 142.0 (±8.3), 138.8 (±11.0), and 145.6 (±9.3) in the TED group, respectively, and 134.9 (±8.7), 133.4 (±10.9), and 139.9 (±8.3) in the control group, respectively. At all three measured points, the AIOS was larger in TED than in controls (P < 0.001); this association remained significant in male and female groups after stratification by sex. Taking the mean of the anterior, middle, and posterior measurements of the AIOS, the average AIOS was 0.21° larger with TED compared to controls after adjusting for age, sex, and race on multivariate analysis (P < 0.001).

Overall, the mean AMW in degrees was smaller in orbits with TED 6.6 (±4.7) compared to controls 7.3 (±4.7) (P = 0.045). On further stratification by sex, Table 2 shows that the association between TED and smaller AMW remained significant in men, although there was no significant association between TED, DON, and proptosis with AIOS or AMW. Generalized estimating equations were used to individually assess the association of TED, DON, and proptosis with AIOS or AMW measurements on univariate analysis. Results for TED were further stratified by sex. Age, sex, and race were also included as covariables to TED on multivariate analysis with AIOS or AMW. Generalized estimating equations were used to individually assess the association of TED, DON, and proptosis with AIOS or AMW. Generalized estimating equations were used to individually assess the association of TED, DON, and proptosis with AIOS or AMW. Generalized estimating equations were used to individually assess the association of TED, DON, and proptosis with AIOS or AMW.

**TABLE 1. Characteristics of the Study Subjects**

<table>
<thead>
<tr>
<th></th>
<th>TED (n = 124)</th>
<th>Control (n = 138)</th>
<th>P Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>46.1 (14.9)</td>
<td>44.0 (21.1)</td>
<td>0.45</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>56 (45.2)</td>
<td>75 (54.3)</td>
<td>0.14</td>
</tr>
<tr>
<td>Female</td>
<td>68 (54.8)</td>
<td>63 (45.7)</td>
<td></td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chinese</td>
<td>95 (76.6)</td>
<td>101 (75.2)</td>
<td>0.89</td>
</tr>
<tr>
<td>Malay</td>
<td>18 (14.5)</td>
<td>23 (16.7)</td>
<td></td>
</tr>
<tr>
<td>Indian</td>
<td>6 (4.8)</td>
<td>9 (6.5)</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>5 (4.0)</td>
<td>5 (3.6)</td>
<td></td>
</tr>
</tbody>
</table>

Data presented as mean (standard deviation) or number (percentage) as appropriate.

* Comparison between TED and control subjects by the Mann-Whitney U test for age and the χ² square test for sex and race.

**TABLE 2. Comparison of the AIOS and AMW Between the TED and Control Groups**

<table>
<thead>
<tr>
<th></th>
<th>TED</th>
<th>Control</th>
<th>P Value‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Both</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AIOS Ant, °</td>
<td>142.0</td>
<td>134.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>AIOS Mid, °</td>
<td>138.8</td>
<td>133.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>AIOS Post, °</td>
<td>145.6</td>
<td>139.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>AMW, °</td>
<td>6.6</td>
<td>7.5</td>
<td>0.045</td>
</tr>
<tr>
<td>Male</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AIOS Ant, °</td>
<td>142.0</td>
<td>136.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>AIOS Mid, °</td>
<td>137.4</td>
<td>132.4</td>
<td>0.003</td>
</tr>
<tr>
<td>AIOS Post, °</td>
<td>145.4</td>
<td>138.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>AMW, °</td>
<td>6.7</td>
<td>8.7</td>
<td>0.004</td>
</tr>
<tr>
<td>Female</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AIOS Ant, °</td>
<td>141.9</td>
<td>133.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>AIOS Mid, °</td>
<td>140.0</td>
<td>134.2</td>
<td>0.001</td>
</tr>
<tr>
<td>AIOS Post, °</td>
<td>145.7</td>
<td>141.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>AMW, °</td>
<td>6.4</td>
<td>6.0</td>
<td>0.70</td>
</tr>
</tbody>
</table>

* n = 248 (112 male, 136 female).

† Comparison between TED and control groups by the Mann-Whitney U test for age and the χ² square test for sex and race.

‡ Comparison between TED and control groups by linear regression models with generalized estimating equations.
between TED and AMW in women. On multivariate analysis adjusting for age, sex, and race, the association of smaller AMW in TED was no longer statistically significant ($\beta = -0.96, P = 0.07$).

Table 3 shows that in TED, the AMW was significantly correlated with the cross-sectional area of the medial rectus measured at the middle and posterior sections and on average. On further subanalysis by sex, these correlations remained significant in men, but not in women. No significant correlation was found between the sum of cross-sectional areas of the four extraocular muscles combined and the AMW. There was also no significant correlation between the AIOS and the cross-sectional areas of the inferior rectus, the medial rectus, or the sum of the four extraocular muscles combined (data not shown).

Further analysis of the orbits in TED patients with and without proptosis and with and without DON revealed no significant difference in the AIOS or AMW measurements between these groups (Table 4).

**DISCUSSION**

Overall, the AIOS was found to be larger and the AMW smaller in patients with TED compared to controls. After adjusting for age and sex, the larger AIOS in TED remained significant, and the trend of smaller AMW in TED was still consistent although no longer statistically significant ($P = 0.07$). In orbits affected by TED, a smaller AMW was also found to correlate with a larger medial rectus muscle. Thus, this study presents evidence that suggests the presence of bony remodeling in TED, where this bony remodeling is possibly related to an increased volume of intraorbital soft tissue content.

The orbital cavity is a pear-shaped enclosed compartment bounded posteriorly and circumferentially by the periorbita and bones, and anteriorly by the orbital septum and globe. Within this enclosed space, the expansion of intraorbital muscle and fat in TED has been shown to be associated with higher intraorbital pressures.\(^{17,18}\) As bone is a dynamic tissue that is constantly renewed, where mechanotransduction is a key mechanism by which remodeling of bone tissue is regulated,\(^{19}\) it has correspondingly been observed that bones of the skull may undergo structural changes in the presence of increased pressure from benign masses\(^{20,21}\) and raised intracranial pressure,\(^{22,23}\) as well as specifically in TED.\(^{24}\)

In the study by Chan et al.,\(^{24}\) which looked at the structure of the orbital apex in TED patients in relation to its association with DON, it was found that an increased muscle bulk was accompanied by a wider angle of the orbital apex. Thus, we postulate that chronically increased intraorbital soft tissue volume and pressure in TED causes bony remodeling of the orbit, which in this study we have attempted to quantify by measuring the AIOS and the AMW.

The convexity of the medial wall was measured in this study as the AMW. Being the thinnest wall of the orbit, the medial wall may be more liable to bony remodeling secondary to raised intraorbital pressures. Prior studies lend support to this hypothesis. Dectorakis\(^ {25}\) presented a case report of a TED patient in whom there was spontaneous medial wall decompression in the presence of massive medial rectus muscle enlargement. Another retrospective case review also found that in patients with TED that had spontaneous medial wall decompression, this was significantly correlated with medial rectus muscle diameter.\(^ {26}\) This is consistent with our data, which show a small but statistically significant correlation between larger medial rectus muscles and smaller AMWs (in men specifically, as discussed below). Of note, no correlation between AMW and the sum of the cross-sectional areas of the four recti muscles was seen. This may suggest that local pressure on the orbital wall from an adjacent enlarged extraocular muscle, rather than a generalized increase in intraorbital soft tissue volume and pressure, may be the driving force behind the remodeling of the bony orbit. In our study, TED was associated with smaller AMWs overall—on further stratification by sex, this association remained consistent in

### Table 3. Correlations Between AMW and Medial Rectus Measurements in TED

<table>
<thead>
<tr>
<th>AMW, (\overline{\text{mm}}^2)</th>
<th>Anterior Medial Rectus</th>
<th>Middle Medial Rectus</th>
<th>Posterior Medial Rectus</th>
<th>Average Medial Rectus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Both</td>
<td>-0.13 (0.17)</td>
<td>-0.22 (0.02)</td>
<td>-0.25 (0.01)</td>
<td>-0.23 (0.01)</td>
</tr>
<tr>
<td>Male</td>
<td>-0.26 (0.06)</td>
<td>-0.36 (0.01)</td>
<td>-0.41 (0.01)</td>
<td>-0.40 (0.01)</td>
</tr>
<tr>
<td>Female</td>
<td>0.03 (0.84)</td>
<td>-0.11 (0.36)</td>
<td>-0.08 (0.54)</td>
<td>-0.06 (0.64)</td>
</tr>
</tbody>
</table>

Data are presented as the weighted Spearman’s rank correlation coefficient (\(P\) value).

**Table 4. Comparisons of The AIOS and AMW Between TED Orbits With and Without DON, or With and Without Proptosis**

<table>
<thead>
<tr>
<th>DON Compared With No DON</th>
<th>Proptosis Compared With No Proptosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>DON, (n = 22)</td>
<td>No DON, (n = 214)</td>
</tr>
<tr>
<td>AIOS Ant, (\overline{\text{mm}}^2)</td>
<td>Mean</td>
</tr>
<tr>
<td>140.5</td>
<td>9.6</td>
</tr>
<tr>
<td>AIOS Mid, (\overline{\text{mm}}^2)</td>
<td>Mean</td>
</tr>
<tr>
<td>141.6</td>
<td>8.4</td>
</tr>
<tr>
<td>AIOS Post, (\overline{\text{mm}}^2)</td>
<td>Mean</td>
</tr>
<tr>
<td>147.7</td>
<td>11.0</td>
</tr>
<tr>
<td>AMW, (\overline{\text{mm}}^2)</td>
<td>Mean</td>
</tr>
<tr>
<td>6.3</td>
<td>5.0</td>
</tr>
</tbody>
</table>

12 and 18 orbits had missing data for the presence of DON or proptosis, respectively, and these cases were excluded for the above analyses.\(^1\)

Comparison between TED orbits with and without DON using linear regression models with generalized estimating equations.\(^1\)

Comparison between TED orbits with and without proptosis using linear regression models with generalized estimating equations.\(^1\)
males, but no significant association was found in females. This mirrors our findings that the smaller AMWs were correlated with larger medial rectus muscles in males, but not in females. As there was no significant difference in the average medial rectus cross-sectional area in women compared to men ($\beta = -2.96$, $P = 0.06$), it is possible that baseline anatomic differences in the AMW between the sexes may account for this difference. In controls, the AMW in women was significantly smaller compared to that in men ($\beta = -1.64$, $P = 0.002$). Thus, the mechanisms of bony remodeling in TED may act less strongly on the medial walls of women, which are already less convex to begin with.

The inferomedial orbital strut (IOS) is a triangular-shaped bony thickening at the junction of multiple orbital bones that form the inferior and medial orbital walls, and acts as a structural support to the orbit and a point of attachment for several muscles that arise from the orbit.27-29 The IOS is a complex three-dimensional structure. Hence, the determination of the IOS volume and its changes in TED is challenging.26,31

Another important consideration with regard to the assumed bony remodeling of the orbit in TED is that bone may also be affected by both hyperthyroidism and therapeutic steroid usage itself. In the adult, biochemical hyperthyroidism increases both bone resorption and formation but overall favors osteoclastic resorption, which over time can lead to secondary osteoporosis.42-44 Furthermore, the cumulative time a patient remains hyperthyroid is a risk factor for major osteoporotic fractures.45-47 The effect of systemic steroids, which may be administered in the treatment of TED, on bone are similar: It may increase bone resorption, reduce osteoblastic activity, and result in osteoporosis in adults.48-50 Thus, in TED, be it due to hyperthyroidism or the effects of treatment with intravenous or oral steroids, a tendency toward microarchitectural weakening in the orbital bones may be a permissive factor that allows for the remodeling of the bone to occur under the stress of an increased intraorbital soft tissue volume and pressure.

The bony remodeling of the orbit in TED would have both diagnostic and therapeutic implications. An orbit with a larger IOS and a more concave medial wall may indicate to the physician a chronicity of increased intraorbital pressures, which has been at least partially relieved through an expansion of the orbital cavity volume—thus, compared to an orbit in which bony remodeling has not taken place, such as in the acute setting of a stormy onset of TED, the risk of compressive complications such as DON may be comparatively lower.51 Additionally, the presence of bony remodeling at the IOS may also have implications for operative technique in surgical decompression, as the preservation of the anterior IOS is crucial in preventing inadvertent postdecompression dystopia.28,29

A few limitations of this study have to be borne in mind when considering the interpretation of the IOS and AMW data. Firstly, it should be understood that both the medial wall and the IOS are complex three-dimensional structures. Hence measuring the AMW in a single plane serves only as a crude approximation of the curvature of the entire medial wall. Similarly, the IOS or the maxillo-ethmoidal junction is generally angular in shape,52 which allows a consistent IOS measurement to be taken; however, when this junction becomes more curved, as it does in TED, the measurement of the “angle” of a curve becomes mathematically imprecise. Secondly, the measurements of extraocular muscle diameters at chosen planes on a CT scan and the calculated cross-sectional muscle area are at best only imperfect approximations of the true muscle volume.16,53 Thus, when we investigate, for example, the relationship between the medial rectus size and the medial wall curvature, the accuracy of the correlation is dependent in turn on how well the calculated cross-sectional area of the medial rectus approximates the true medial rectus muscle volume, and how well the AMW describes the total curvature of the medial wall. Thirdly, measuring the diameters and calculated areas of the four recti muscles only incompletely describes the increase in intraorbital tissue volume, as it fails to account for the other two oblique muscles and the intraorbital fat compartment. As has been shown by Regensburg et al.,34 different subtypes of TED may be distinguished: no fat or muscle volume increase,
either fat or muscle volume increase, or both fat and muscle volume increase.

With the description of the AIOS and AMW radiologic parameters in this study, future studies would do well to quantify the volumes of the orbital cavity in TED and controls, and whether the volume measurements correlate well with the AIOS and AMW parameters. A prospective radiologic study would also aid in defining the concept of bony remodeling of the orbit in TED.

In conclusion, a difference in the structure of the bony orbit in TED compared to controls may be demonstrated by the AIOS and AMW radiologic parameters. This likely represents the presence of bony remodeling in TED. Prior case reports and a case series have previously proposed the concept of a drastic and sudden auto-decompression that may occur spontaneously from fractures of either the medial wall or orbital floor in TED\textsuperscript{25,26,39,40}; such events, though, might be uncommon. Here, we demonstrate evidence that suggests a more graded and presumably gradual auto-decompression that occurs commonly in TED. With the AMW being smaller in TED orbits with larger medial rectus muscles, this bony remodeling may be related to the expansion of the intraorbital soft tissue volume.

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