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Abstract. The purpose of this study is to understand the phenotypes of thyroid eye disease (TED) through data derived from a multiatlas segmentation of computed tomography (CT) imaging. Images of 170 orbits of 85 retrospectively selected TED patients were analyzed with the developed automated segmentation tool. Twenty-five bilateral orbital structural metrics were used to perform principal component analysis (PCA). PCA of the 25 structural metrics identified the two most dominant structural phenotypes or characteristics, the “big volume phenotype” and the “stretched optic nerve phenotype,” that accounted for 60% of the variance. Most of the subjects in the study have either of these characteristics or a combination of both. A Kendall rank correlation between the principal components (phenotypes) and clinical data showed that the big volume phenotype was very strongly correlated (p -value <0.05) with motility defects, and loss of visual acuity. Whereas, the stretched optic nerve phenotype was strongly correlated (p -value <0.05) with an increased Hertel measurement, relatively better visual acuity, and smoking. Two clinical subtypes of TED, type 1 with enlarged muscles and type 2 with proptosis, are recognizable in CT imaging. Our automated algorithm identifies the phenotypes and finds associations with clinical markers. © 2018 Society of Photo-Optical Instrumentation Engineers (SPIE) [DOI: 10.1117/1.JMI.5.4.044001]

Keywords: thyroid eye disease; computed tomography; orbit; multiatlas; label fusion; segmentation; principal component analysis.

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1 Introduction

Thyroid eye disease, or Grave’s ophthalmopathy, is a condition that affects muscles and other soft tissues in the eye orbits. It is most often associated with Grave’s disease, an autoimmune disorder causing hyperthyroidism. Computed tomography (CT) imaging of the orbit is the standard clinical practice in the diagnosis and management of thyroid eye disease (TED).¹

CT imaging shows distinct structures in the eye orbit, such as globes, the optic nerve, extra ocular rectus muscles, and orbital fat. Previous studies have shown that volumetric and structural measurements of these structures are strongly associated with TED characteristics and risk for optic nerve pathologies.^{2–9} However, these studies relied on manual measurements on orbital structures and subjective clinical criteria for description of TED.^{10,11} There is also clinical literature that hypothesized that TED had distinct phenotypes based on clinical and orbital structural characteristics.^{12–14} In this work, we use an automated pipeline to extract metrics from CT imaging to investigate the phenotypes of TED based on measurements of the optic nerve, extraocular muscle volume, and orbital volume and crowding.

The automated segmentation pipeline that identifies structures of interest, namely the globe, the optic nerve, the superior, inferior, lateral and medial extraocular muscles, and orbital fat is based on previous work by Harrigan et al.¹⁵ and Chaganti et al.¹⁶ We extract structural measurements from the automated segmentation and perform statistical analysis on them to learn phenotypes of action in TED. We then evaluate how these

phenotypes are correlated with clinical factors such as visual acuity, color vision, history of smoking, and so on.

The main contribution of this work is the identification of the two main orthogonal phenotypes of action. The factor loadings of the top two principal components of the imaging metrics correspond to the descriptions hypothesized in the clinical literature by Nunery.¹² Finally, we empirically show that these two phenotypes correspond to different clinical losses, such as visual loss and proptosis, respectively.

2 Methods

Eighty-five patients were retrospectively selected from Vanderbilt University Medical Center (VUMC) who had orbital CT imaging performed before any surgical intervention for TED, after exclusion criteria for imaging issues, such as severe artifact and low resolution. Institutional Review Board approval was obtained at Vanderbilt University. CT Imaging and clinical information including visual disability testing and demographic information were recorded.

2.1 CT Data

The selected patients underwent CT imaging of the eye orbits as part of the regular clinical care; as a result the acquisition parameters are highly heterogeneous. The selected imaging had variable imaging protocols including CT head, orbital, and maxillofacial. However, for all imaging scans the field of view included the full optic nerves from the globes to the chiasm, and the complete view of orbital structures of interest

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such as extraocular rectus muscles bilaterally. The window size of the scans was 512×512 . Each scan had an average of 65 slices with a thickness of 2 mm (± 0.95 mm). The average in-plane resolution was 0.35×0.35 mm (± 0.05 mm). The data were retrieved in a deidentified form under institutional review board approval in a manner that removed the identification of the clinical imaging devices for each scan. The images were acquired clinically at VUMC, which uses a variety of settings and scanners from Philips, GE, Picker, and Marconi. For each of the 85 selected patients, the highest resolution scan predecompression surgery was manually selected.

2.2 Clinical Data

Clinically pertinent information was recorded for each patient such as age, sex, and visual disability testing. Eight measures of visual disability were recorded: logmar vision, color vision, best corrected visual acuity, AMA defined visual acuity score, visual field score, functional acuity score, functional field score, and functional vision score.¹⁷ Clinical measures indicating the severity of the disease were collected, such as Hertel measurements, which describe the amount of proptosis,^{18,19} ocular motility defects indicating difficulty in eye movement due to enlarged muscles,⁶ and the presence of optic neuropathy, which is indicative of optic nerve involvement.^{20,21} In addition, the smoking history of each patient was recorded as it is known to be highly associated with TED.^{13,22} Table 1 shows the list of clinical characteristics used for the analysis. The clinical data was available for all the patients at the time of the CT scan with the exception of three patients. The closest available clinical notes within 6 months were referred for these three patients.

Table 1 Clinical characteristics.

Clinical measure	Description (assessment metrics)
Logmar visual acuity	Visual acuity using logmar chart (−0.3 to 1)
Color vision	Ability to distinguish color. (0 to 20)
Best corrected visual acuity	Visual acuity with best possible lens correction denominator (20/10 to 20/200)
Visual acuity score	AMA defined visual acuity score (0 to 100)
Functional acuity score	Weighted visual acuity score (0 to 100)
Visual field score	AMA defined visual field perception score (0 to 100)
Functional field score	Weighted visual field score (0 to 100)
Visual function score	Percentage of ability when compared to healthy control (0 to 100)
Hertel measurement	Measurement of proptosis using a Hertel exophthalmometer (in mm)
Ocular motility defects	Presence of difficulties in eye movement (0—absent/1—present)
Optic neuropathy	Presence of optic neuropathy (0—absent/1—present)
Smoking history	History of smoking (0—non-smoker, 1—former smoker, and 2—current smoker)

Fig. 1 Image processing flowchart.

2.3 Image Processing

Figure 1 shows the image-processing pipeline. First, a three-step multiatlas segmentation algorithm was employed to identify the orbital structures of interest. In the multiatlas paradigm, a set of expertly labeled example CT atlases are used as training examples to obtain the segmentation from a new target CT atlas.¹⁵ The

Table 2 Structural metrics.

Metric #	Structural metric
Size/Volumetric measurements	
1 to 5	Superior, inferior, lateral, medial rectus, and total muscle volumes
6 to 9	Superior, inferior, lateral, medial rectus muscle maximum diameter
10 to 13	Superior, inferior, lateral, medial rectus muscle average diameter
14	Globe volume
15	Globe diameter
16	Optic nerve volume
17 to 18	Optic nerve length and traditional length
19	Optic nerve average area
20	Optic nerve maximum diameter
21	Orbital volume
Crowding indices	
22	Barrett's index
23	Volumetric crowding index
Orbital structure metrics	
24	Degree of proptosis
25	Orbital angle

clinical imaging that we obtained contains several imaging protocols with variable fields of view ranging from orbital to head CT. The first step involves localizing the eye orbit in the target scan and cropping a region around the orbit, so that the target image has the same field of view as the atlases used for label fusion. To do so, the example atlases are rigidly registered to the target image and the corresponding labels are propagated to the target space using NiftyReg.²³ Next, the masks of the rigidly registered atlases are summed to construct a probability map that provides an approximate location of the eye orbit. A padded region of voxels having >0.5 probabilities is selected for cropping. The second step involves using nonrigid registration to register the cropped example atlases to the cropped target image obtained from step 1 using ANTS SyN.²⁴ The corresponding labels of the example atlases are propagated to the target space using the nonrigid deformations. Step 3 involves

fusing the transformed labels in step 2, using nonlocal statistical label fusion^{25,26} to obtain the final segmentation of the eye globe, the optic nerve, the extraocular muscles, and the orbital fat. The identification of the individual extraocular muscles using label fusion is difficult in diseased eyes due to crowding at the orbital apex. Kalman filters were used to segment muscle labels obtained from the multitlas algorithm into individual extraocular muscles: the superior rectus, the inferior rectus, the medial rectus, and the lateral rectus muscle.¹⁶ At each coronal slice, we use four Kalman filters to track each of the four rectus muscles from the anterior to posterior direction starting at the front of the eye where the muscles are well separated. The globe and the optic nerves pass through the center of the orbit and are used as landmarks at each coronal slice to help identify the muscle positions. A fifth Kalman filter is used to track landmarks from anterior to the posterior coronal slice.

Fig. 2 (a) CT imaging of the head showing full view of the eye orbit. (b) Result of segmentation showing: eye globes, optic nerve, orbital fat, superior rectus muscle, inferior rectus muscle, lateral rectus muscle, and medial rectus muscles.

Fig. 3 (a), (b), and (c) show examples of clinically acquired CT scans with different fields of view and positions. (d), (e), and (f) show the results of the segmentation pipeline for these images.

	Comp 1	Comp 2	Comp 3	Comp 4	Comp 5	Comp 6	Comp 7	Comp 8	Comp 9	Comp 10	Comp 11	Comp 12
Explained variance	46.3%	13.0%	10.1%	6.5%	4.7%	4.0%	3.7%	3.0%	2.5%	1.4%	1.3%	0.9%
Superior muscle volume	0.24	0.02	0.13	0.24	0.08	0.39	0.02	0.11	0.01	0.06	0.14	-0.11
Inferior muscle volume	0.25	0.14	0.02	0.13	0.04	0.03	0.05	0.16	0.11	0.34	-0.09	-0.24
Lateral muscle volume	0.26	0.08	0.20	0.07	0.13	0.04	0.23	0.15	0.14	-0.29	0.07	-0.15
Medial muscle volume	0.26	0.05	0.04	0.08	0.08	0.18	0.35	0.14	0.03	-0.03	0.11	-0.23
Superior muscle DiameterAvg	0.23	0.07	0.08	0.22	0.03	0.42	0.09	0.09	0.05	-0.08	-0.05	-0.15
Inferior muscle DiameterAvg	0.24	0.08	0.07	0.22	0.07	0.09	0.11	0.27	0.12	0.31	-0.22	-0.08
Lateral muscle DiameterAvg	0.24	0.01	0.23	0.09	0.12	0.05	0.25	0.13	0.11	-0.26	0.09	-0.15
Medial muscle DiameterAvg	0.23	0.10	0.04	0.09	0.12	0.24	0.38	0.11	0.09	-0.11	0.04	-0.17
Superior muscle DiameterMax	0.21	0.10	0.14	0.20	0.01	0.47	0.02	0.04	0.15	-0.20	-0.27	0.28
Inferior muscle DiameterMax	0.20	0.13	0.15	0.29	0.01	0.07	0.16	0.19	0.08	0.22	-0.29	0.36
Lateral muscle DiameterMax	0.22	0.06	0.25	0.14	0.09	0.02	0.19	0.20	0.10	-0.31	0.05	0.26
Medial muscle DiameterMax	0.22	0.13	0.07	0.02	0.07	0.13	0.50	0.22	0.01	-0.23	-0.02	0.32
Total muscle volume	0.29	0.05	0.05	0.02	0.03	0.06	0.02	0.03	0.03	0.00	0.07	-0.20
Barrett index	0.17	0.03	0.25	0.23	0.07	0.12	0.21	0.59	0.04	0.39	0.44	0.21
Globe volume	0.11	0.06	0.52	0.39	0.04	0.05	0.07	0.05	0.01	-0.09	0.04	-0.05
Globe diameter	0.11	0.07	0.51	0.38	0.04	0.07	0.07	0.06	0.03	-0.09	0.04	-0.02
ON length	0.14	0.33	0.06	0.16	0.19	0.28	0.28	0.20	0.59	-0.21	-0.08	0.16
ON length traditional	0.10	0.44	0.06	0.19	0.18	0.17	0.02	0.07	0.10	0.05	-0.10	-0.17
ON volume	0.23	0.13	0.10	0.25	0.21	0.25	0.16	0.05	0.14	0.21	0.02	-0.04
ON Avg area	0.20	0.29	0.06	0.19	0.16	0.22	0.15	0.10	0.18	0.15	0.04	0.08
ON Max diameter	0.16	0.35	0.07	0.17	0.16	0.21	0.11	0.17	0.00	0.15	0.02	0.37
Orbital volume	0.18	0.29	0.32	0.02	0.04	0.04	0.12	0.23	0.12	-0.01	0.40	0.17
Volumetric crowding index	0.13	0.38	0.08	0.22	0.01	0.06	0.19	0.27	0.10	-0.04	-0.40	-0.25
Proptosis	0.07	0.30	0.16	0.18	0.48	0.16	0.13	0.26	0.48	0.15	-0.43	0.14
Angle	0.01	0.18	0.06	0.21	0.72	0.04	0.10	0.22	0.47	0.19	0.12	-0.03
Scale	1	0.8	0.6	0.4	0.2	0	-0.2	-0.4	-0.6	-0.8	-1	-1

Fig. 4 Distribution of individuals along the top two components identified by PCA. Each point represents one individual. Males are coded as red and females as white. The x-axis represents phenotype 1 that shows variation in muscle volume, and the y-axis shows variation in ON length and volume.

Once the final segmentation is obtained, the image-processing pipeline computes 25 structural metrics bilaterally, describing the sizes and structural arrangements of the eye orbit. The complete list of metrics is shown in Table 2. For each structure, the volume, cross-sectional area, and diameter/length are measured.^{5,6,27–33} Indices of orbital crowding, i.e., Barrett's muscle index⁴ and volumetric crowding index,⁸ are computed. In addition, degree of proptosis³⁴ and orbital angle is computed.⁷

2.4 Statistical Analysis

First, outlier points that fall outside of the two standard deviations of the mean were discarded for each of the structural metrics shown in Table 2, which were extracted from the image segmentation pipeline. Each metric is standardized by subtracting its mean value and dividing the difference by its standard deviation. Principal component analysis (PCA) is performed on the standardized metrics. Next, a Kendall rank

correlation was performed between the principal components of image metrics and clinical factors shown in Table 1.

A rank correlation was used because several associations can be nonlinear; however, the relative change in clinical measures with changes in structural metrics is important to note. The significance of the correlation is computed using a permutation distribution of the correlation coefficient, which has the expected value of 0 under null hypothesis.

3 Results

The image processing pipeline produced segmentations of orbital structures in the eye: the eye globe, the optic nerve, the superior rectus muscle, the inferior rectus muscle, the lateral rectus muscle, and the medial rectus muscle, and the orbital fat. Figure 2 shows the three-dimensional (3-D) segmentations obtained from this pipeline. Figure 3 shows additional examples of the result for patients with different fields of view and head positions. Twenty-five structural metrics are computed from these segmented structures.

3.1 PCA of Structural Metrics: TED Subtypes

The 25 structural metrics obtained from CT imaging are used to perform a PCA. Figure 4 shows the factor loadings of the metrics for top 12 components that explain 97% of the variance. The top two components, which explain over 60% of the total variance, show two distinct clusters of metrics. Component 1 shows characteristics with large size and volume measurements of the extraocular muscles. Component 2 shows longer and thinner optic nerves with increased orbital fat (volumetric crowding index is lower). These two clusters of structural metrics align with Nunery's classification of TED subtypes.^{12–14} Nunery describes a subtype of TED patients with motility defects and enlarged extraocular muscles (component 1 or type 1) and a subtype without motility defects and increased orbital fat (component 2 or type 2). Examples of the two subtypes of segmented labels are shown in Fig. 5. However, there is a high variability in the presentation of the phenotypes in individual patients. Each individual can express either, both or none of the phenotypes to varying degrees. Figure 6 shows the distribution of patients by phenotype and sex.

3.2 Correlation Subtypes of TED and Clinical Characteristics

The top two components corresponding to the two major subtypes of TED are crossed with the 12 clinical characteristics as shown in Table 3.

Component 1, with enlarged extraocular muscles, is highly correlated with ocular motility ($p < 0.05$) as postulated by Nunery. It is also associated with vision loss (logmar visual acuity and AMA visual acuity score).

Component 2, with longer and thinner optic nerve and higher orbital fat, does not correlate with ocular motility issues also aligning with Nunery's description. Component 2 is correlated ($p < 0.05$) with Hertel measurements indicating that this group has more proptosis. Component 2 is negatively correlated with vision loss, indicating relatively low effects on vision compared with component 1. A positive smoking history is associated with component 2.

Fig. 5 Factor loadings of 12 principal components of the structural metrics explaining 97.46% of the variance. The top two principal components are enclosed in a red box. Positive loadings are green, and negative loadings are red.

Fig. 6 Subtypes of TED. (a) Example of subtype 1 showing big muscles—with high values along component 1. (b) Example of subtype 2 showing longer and thinner optic nerve, and greater orbital fat—with high values along component 2.

4 Discussion

TED is a serious condition that can lead to temporary or permanent loss of vision in some patients.^{35,36} Often, the clinical manifestations or characteristics of the disease can be confounding and variable in presentation. CT imaging is often used clinically, to make diagnostic and prognostic evaluations. An objective and quantitative assessment of the CT imaging and their related clinical characteristics can improve diagnosis and intervention.

In this study, we established a new quantitative method to identify characteristics of TED through clinically acquired CT

Table 3 Kendall rank correlation between clinical characteristics and the top two principal components representing the two phenotypes of thyroid of disease. Component 1 represents bigger muscle phenotype. Component 2 represents longer and thinner optic nerve.

Clinical characteristics	Comp 1	Comp 2
Logmar visual acuity	0.14***	−0.08
Color vision	−0.07	0.05
Best corrected visual acuity	0.13*	−0.23***
Visual acuity score	−0.16***	0.15*
Functional acuity score	−0.15	0.16***
Visual field score	−0.04	0.16***
Functional field score	−0.04	0.14*
Functional vision score	−0.10	0.18***
Hertel measurement	−0.01	0.35***
Motility defect	0.17***	0.07
Optic neuropathy	−0.03	−0.07
Smoking	0.08	0.16***

*Moderately significant correlations ($p < 0.1$).

***Highly significant correlations ($p < 0.05$).

imaging by showing that an automated pipeline can be used to segment structures of importance and extract structural metrics.

We developed a method to identify the two important subtypes of TED from CT imaging. Though these subtypes have been described in terms of their clinical manifestations and through manual measurements of CT imaging, our study is the first to show the presence of these subtypes through a quantitative procedure by computing principal components on structural CT metrics and computing Kendall rank correlations with clinical characteristics. Because of high biological variability, the Kendall rank correlations observed between clinical measures and the principal components are low. However, the correlations are statistically significant and objectively establish associations observed in clinical literature such as: type 1 is associated with ocular motility, whereas type 2 is not;^{6,37,38} type 1 is associated with more severe vision loss than type 2;³⁹ type 2 is associated with increased proptosis;¹³ and type 2 is associated with smoking.⁴⁰

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