



Corneal, Scleral, Choroidal, and Foveal Thickness in Patients with Rheumatoid Arthritis

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Abstract

Objectives: To investigate corneal, scleral, choroidal, and foveal thicknesses in female patients with rheumatoid arthritis (RA) and compare them with healthy subjects.

Materials and Methods: This prospective study included consecutive female patients diagnosed with RA and healthy subjects. Corneal, scleral, choroidal, and retinal (foveal) thicknesses were obtained by using optical coherence tomography and a comparison was performed between groups for all outcome measures.

Results: Thirty-six eyes of 36 female patients diagnosed with RA (group 1) and 36 eyes of 36 healthy female volunteers (group 2) were included. Mean corneal, scleral, choroidal thicknesses and retinal thickness at the fovea of group 1 were $543.3 \pm 33.7 \mu\text{m}$, $343.7 \pm 42.2 \mu\text{m}$, 214.6 ± 50 , and $213.5 \pm 18.9 \mu\text{m}$, respectively; in group 2, these values were $549.9 \pm 29.6 \mu\text{m}$, $420.9 \pm 42.4 \mu\text{m}$, $206.4 \pm 41.9 \mu\text{m}$, and $222 \pm 15.5 \mu\text{m}$, respectively. The comparison between group 1 and 2 with respect to corneal, choroidal, and foveal thicknesses did not reveal statistical significant differences ($p > 0.05$). On the contrary, there was a statistically significant difference with respect to scleral thickness between the groups, with the RA patients demonstrating a thinner scleral layer ($p < 0.001$).

Conclusion: Female patients with RA seem to demonstrate statistically significant scleral thinning when compared with healthy subjects, while there was no difference concerning corneal, choroidal, and foveal thickness.

Keywords: Rheumatoid arthritis, scleral thickness, corneal thickness, choroidal-retinal thickness, optical coherence tomography

Introduction

Rheumatoid arthritis (RA) is a systemic inflammatory disease which primarily affects the joints and may also manifest with extra-articular symptoms.¹ Ocular manifestations can be found in 25% of patients with RA, and include keratoconjunctivitis sicca, peripheral corneal ulceration, keratitis, episcleritis, scleritis, choroiditis, and retinal detachments.^{2,3} Patients with RA not treated with effective immunosuppressive therapy may develop peripheral ulcerative keratitis, necrotizing scleritis, corneal and

scleral perforations, which may lead to visual function decrease and thereby seriously reduce patients' quality of life.⁴

Scleral inflammation caused by RA can manifest as mild episcleritis or full-thickness scleritis, which can rarely result in scleral melting.⁵ Scleral thickness has been measured in previous studies with ultrasound biomicroscopy as well as with anterior segment optical coherence tomography (OCT) in glaucomatous patients. In this study we assessed scleral thickness using OCT in patients with RA and compared them with healthy volunteers. Furthermore, we also utilized enhanced depth imaging (EDI)-

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OCT, which is a newer technique allowing cross-sectional imaging of the retina and choroid. EDI-OCT and anterior segment OCT have been used to evaluate retinal and choroidal thickness in many ophthalmic diseases; however, there is a lack of studies investigating patients with RA.^{6,7} The current study prospectively investigated corneal, scleral, choroidal, and foveal thicknesses in female patients with RA and compared the outcomes with healthy female subjects.

Materials and Methods

Patient Population

This prospective study included female patients that were diagnosed with RA in accordance with the 2010 RA classification of the American Rheumatism Association in the Rheumatology Department of Başkent University in Ankara, Turkey between June and December 2014. Two groups of subjects were assessed in this study; group 1 included eyes of female patients diagnosed with RA and group 2 consisted of eyes of healthy female subjects.

The study was approved by the Başkent University Institutional Review Board and Ethics Committee (KA 14/26). The research adhered to the tenets of the Declaration of Helsinki, and detailed written informed consent was obtained before each individual's participation in the study.

Inclusion and Exclusion Criteria

Female patients over the age of 45 years with positive rheumatoid factor and were diagnosed with RA in accordance with the 2010 RA classification of the American Rheumatism Association were included in the study. In order to avoid refractive error magnitude influencing the main outcome measures (corneal, choroidal, and scleral thickness), we included patients with spherical refractive error between +2 and -2 diopters. Exclusion criteria included any corneal or lenticular opacity other than mild cataract, history of trauma or surgery that involved the conjunctiva or sclera, and history of any other connective tissue disease. Patients with active or resolved scleritis, episcleritis, keratitis, or uveitis or any history of these were excluded.

Patient Assessment

The participants underwent a complete ophthalmological examination which included slit-lamp clinical evaluation of the central cornea, perilimbal sclera, central retina, and choroid. Corneal and scleral thickness was measured using the Cirrus HD-OCT (Carl Zeiss Meditec, Dublin, CA, USA); choroidal and foveal thicknesses were measured using the Heidelberg Spectralis OCT (Heidelberg Engineering, Heidelberg, Germany). Corneal thickness measurements were obtained with the eyes in primary gaze position, while scleral thickness measurements were obtained using a 45° temporal gaze to measure the sclera 2 mm nasal to the corneal limbus (Figures 1 and 2).

Choroidal thickness was measured perpendicularly from the outer edge of the retinal pigment epithelium (RPE) to the choroid/scleral boundary at the fovea and at 6 more points located at 1000 µm nasal to the fovea, 2000 µm nasal to the fovea, 3000 µm nasal to the fovea, 1000 µm temporal to the fovea, 2000

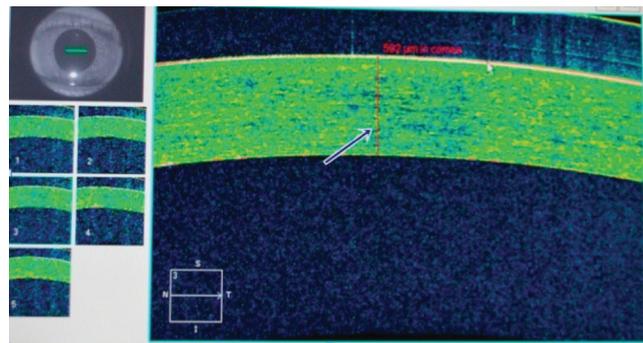


Figure 1. Corneal thickness measurements were obtained during straight gaze position with optical coherence tomography

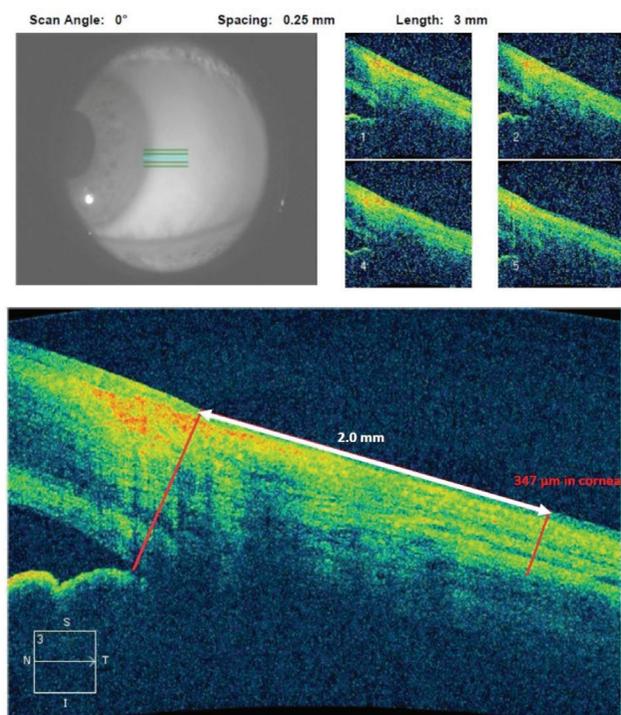


Figure 2. Scleral thickness measurements were obtained during 45 degree temporal gaze position with optical coherence tomography

µm temporal to the fovea, and 3000 µm temporal to the fovea. Retinal thickness was also measured manually from the internal limiting membrane to the RPE at the fovea (Figure 3) using the caliper provided by OCT software. All measurements were taken by two independent blind researchers (O.G. and S.G.G.) and were averaged for statistical analysis. Participants were asked not to consume drinks containing caffeine and/or eat chocolate three hours prior to OCT assessment to avoid possible effects on choroidal thickness.

Statistical Analysis

Statistical analysis was performed using SPSS version 20.0 (Statistical Package for the Social Sciences) software. For each variable, normality was checked by Kolmogorov-Smirnov and Shapiro-Wilk tests. Mann-Whitney U test was used to evaluate

statistical differences in corneal, scleral, retinal, and choroidal thicknesses between groups 1 and 2. Correlation analysis between disease duration and measurements of scleral and corneal thicknesses were performed by using Spearman's Rho test. Values of $p < 0.05$ were considered statistically significant.

Results

This prospective study included a total of 72 eyes of 72 female patients. Group 1 comprised 36 eyes of 36 female RA patients aged 56.12 ± 9 years (range, 45-69 years); group two comprised 36 eyes of 36 healthy females aged 58.13 ± 8 (range, 45-68 years). Therefore, a total of 86 measurements were done; however, 14 measurements were excluded due to poor image quality. All the RA patients were under immunosuppressive therapy and were followed regularly by their rheumatologists. Disease duration after initial diagnosis in the study group (group 1) was 8.6 ± 1.2 years (median 5.5, range 2-40 years). The groups showed no significant difference in age ($p > 0.05$).

Mean corneal thickness was $543.3 \pm 33.7 \mu\text{m}$ (range, 444-612 μm) in group 1, and $549.9 \pm 29.6 \mu\text{m}$ (range, 496-596 μm) in group 2; there was no statistical difference between the groups ($p > 0.05$). Mean scleral thickness was $343 \pm 42.2 \mu\text{m}$ (range, 268-596 μm) in group 1 and $420.9 \pm 42.4 \mu\text{m}$ (range, 354-544 μm) in group 2. The difference between the groups was statistically

significant ($p < 0.01$). Mean retinal thickness as measured from the fovea to RPE was $213 \pm 18.9 \mu\text{m}$ (range, 153-249 μm) in group 1 and $222 \pm 15.5 \mu\text{m}$ (range, 180-256 μm) in group 2; the difference was not statistically significant ($p > 0.05$) (Table 1). Mean choroidal thickness was averaged from seven points at 1000 μm intervals from temporal to nasal choroid across the fovea. The differences between the two groups were not statistically significant ($p > 0.05$) (Table 2). No correlation was

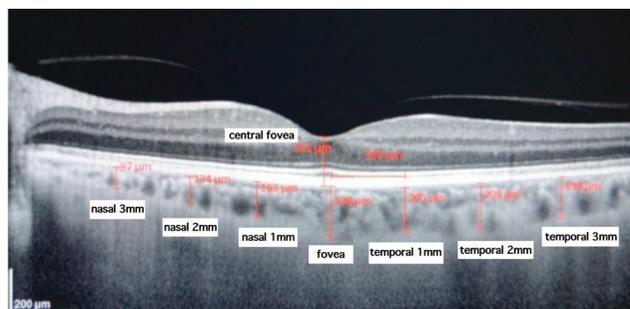


Figure 3. Measurement of choroidal thickness with enhanced depth imaging-optical coherence tomography from the outer edge of the retinal pigment epithelium (RPE) to the choroid/scleral boundary at the fovea and at 6 more points located at 1 mm nasal to the fovea, 2 mm nasal to the fovea, 3 mm nasal to the fovea, 1 mm temporal to the fovea, 2 mm temporal to the fovea, and 3 mm temporal to the fovea. Retinal thickness was measured from the internal limiting membrane to the RPE at the fovea

Table 1. The mean and median corneal, scleral and foveal thicknesses of patients and controls

	Group 1 (in μm)		Group 2 (in μm)		P
	Mean \pm SD	Median (minimum-maximum)	Mean \pm SD	Median (minimum-maximum)	
Cornea	543.3 ± 33.7	542 (444-612)	549.9 ± 29.6	550 (496-596)	0.388
Sclera	343.7 ± 42.2	332 (268-596)	420.9 ± 42.4	420 (345-544)	0.001
Fovea	213.5 ± 18.9	218 (153-249)	222 ± 15.5	222 (180-256)	0.68

SD: Standard deviation

Table 2. The mean and median choroidal thicknesses of patients and controls at 7 points

	Mean \pm SD (in μm)		Median (minimum-maximum) (in μm)		P
	Group 1	Group 2	Group 1	Group 2	
Nasal 3 mm	153.9 ± 48.6	154 ± 43.8	155 (56-284)	158 (70-248)	0.954
Nasal 2 mm	195.0 ± 54.6	188.4 ± 52.3	197 (86-314)	196 (90-337)	0.608
Nasal 1 mm	227.6 ± 64.0	221 ± 50.6	226 (95-438)	226 (124-345)	0.822
Foveal	261.5 ± 61.8	254.4 ± 56.7	258 (107-445)	238 (145-402)	0.270
Temporal 1 mm	239.5 ± 58.3	226.9 ± 58.4	233 (102-428)	217 (129-469)	0.130
Temporal 2 mm	220.7 ± 46.3	207 ± 53.2	211 (116-365)	197 (109-331)	0.139
Temporal 3 mm	200.8 ± 56.5	192 ± 50.2	192 (104-457)	190 (104-338)	0.652
Average	214.6 ± 50.4	206.4 ± 41.9	206 (95-362)	106 (112-295)	0.517

SD: Standard deviation

found between disease duration and corneal thickness or scleral thickness ($p=0.316$).

Discussion

RA is usually associated with extra-articular findings. Turesson et al.⁸ evaluated 609 RA patients from 1955 to 1994 and showed that 247 patients (41%) had at least one extra-articular finding. The most frequent ocular manifestation of RA is keratoconjunctivitis sicca.⁸ Other reported ocular complications of RA are episcleritis, scleritis, retinal vasculitis, peripheral ulcerative keratitis, and interstitial keratitis.⁹ Cytokines such as interleukin 1 (IL-1), IL-6, and tumor necrosis factor alpha (TNF- α) are believed to play a major role in the development of extra-articular findings in RA. The efficacy of anti-TNF- α agents like infliximab further support this hypothesis.¹⁰ An imbalance of these pro- and anti-inflammatory cytokines creates a microenvironment that supports the breakdown of collagen in RA. This can manifest as keratitis starting from the perilimbal cornea and spreading toward the central cornea, causing corneal melting and perforations.^{11,12}

The mechanisms of action of RA suggest that manifestations in different ocular tissues and macrostructural tissue changes (pachymetric alterations, etc.) could occur in patients with RA. In our study we assessed corneal, scleral, choroidal, and foveal thickness in order to identify possible implications of RA on macrostructural tissue alterations with respect to thickness. According to the literature, most of the studies have measured central corneal thickness in RA patients using confocal microscopy, pachymetry, Scheimpflug imaging systems, and ocular response analyzers. However, none of them utilized OCT.^{13,14,15,16} Therefore, we aimed to measure central corneal thickness using anterior segment-OCT in RA patients and we did not detect a statistical significant difference between patients with RA and healthy subjects with respect to central corneal thickness. This finding may suggest that patients actively managed with immunomodulatory agents (like the RA patients in this study) do not demonstrate corneal thinning.

The choroidal layer is the most vascularized layer in the eye, so it can play a role in many ophthalmologic diseases. Newly developed OCT applications (EDI-OCT) allowing cross-sectional imaging of the choroid, and several studies have demonstrated that choroidal thickness changes in ocular diseases such as age-related macular degeneration, high myopia, chorioretinal atrophies, Vogt-Koyanagi-Harada disease, Behçet's disease, sarcoidosis uveitis, and polypoidal choroidal vasculopathy.^{6,17,18} Despite improvements in software analysis, studies have also shown that manual retinal and choroidal thickness measurements are still superior to automated measurements.^{19,20} In the current study we measured choroidal and retinal thicknesses of RA patients manually with the caliper provided by the Spectralis OCT software. According to our results, there was no statistically significant difference with respect to choroidal and retinal thickness when compared to healthy subjects. As our patients were all under active immunomodulatory treatment, this may

have prevented choroidal tissue alterations; possible changes in choroidal thickness may be evident in patients with uncontrolled RA. Nevertheless, choroidal involvement is rare in RA; it is usually a finding after inflammation due to posterior scleritis, which in turn is also rare. Therefore, immunosuppressive treatment may not be the reason for this, as retinal changes are very rare in RA. Given that the current study has a small sample size, the absence of structural changes of the retina may not be indicative. Further studies including patients with uncontrolled RA are needed to investigate the effect of RA on the choroid.

Scleritis in RA has a reported prevalence of 0.63-0.67%. Furthermore, scleral thinning and perforation due to inflammatory vasculitis or scleromalacia perforans rarely occurs in patients with RA.²¹ While scleritis may lead to scleral thinning and melting, the pathogenesis of scleritis in RA is still unknown.²² In our study, although none of our RA patients had active scleritis, inflammatory vasculitis, or scleromalacia perforans, they demonstrated a significant decrease in scleral thickness when compared to the healthy subjects ($p<0.001$). The etiology of this thinning is unclear but may be related to subclinical immune complex deposition and destruction of scleral tissues despite appropriate immunosuppressive therapy. In addition, we evaluated scleral thickness as correlated to disease duration and found no correlation between them. However, the disease progression rate can be quite variable, and the small size of our study may have affected this correlation.

Study Limitations

A limitation of the current study is the small number of eyes included. Furthermore, there is a selection bias with respect to the gender included in the study; we only included female patients as the number of male patients was very small. Our inability to include more male patients can be attributed to the 3-fold higher incidence of RA in the female population when compared to males.²³ Another limitation of the current study is the lack of a positive control (a group of subjects with diseases other than RA that manifest with scleritis). This would add to the current study and provide further scientific validation of the outcomes described herein. We only included a normal (healthy) group of female patients that served as controls, as we did not locate a sufficient number of subjects with diseases other than RA that manifest with scleritis. Finally, the images acquired by the Cirrus HD-OCT are not of high resolution and quality due to the capabilities of the current imaging platform; nevertheless, pachymetric measurements should not be influenced by this limitation.^{24,25}

Conclusion

This study shows that scleral thinning occurs in female patients with RA under active immunomodulatory treatment and no active scleritis, inflammatory vasculitis, or scleromalacia. This could be caused by a chronic inflammatory process, subclinical immune complex deposition, or direct destruction of scleral tissues by autoimmune reaction. Patients with RA could be followed for possible scleral thinning and perforations as there

seems to be a tendency towards thinning despite appropriate immunomodulatory control. Corneal, retinal, and choroidal thicknesses, however, should be normal in properly treated patients.

Ethics

Ethics Committee Approval: The study was approved by the Başkent University Institutional Review Board and Ethics Committee (KA 14/26).

Informed Consent: All volunteers went through a complete informed consent process.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Ahmet Akman, Sirel Gür Güngör, Ahmet Eftal Yücel, Hilmi Yeşil, **Concept:** Ahmet Akman, **Design:** Nilüfer Yeşilirmak, **Data Collection or Processing:** Onur Gökmen, **Analysis or Interpretation:** Fatih Yıldız, Adam Sise, Vasilios Diakonis, **Literature Search:** Onur Gökmen, Nilüfer Yeşilirmak, **Writing:** Onur Gökmen.

Conflict of Interest: No conflict of interest was declared by the authors.

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References

- Ooi KG, Wingate R, Adler PA. Necrotizing anterior scleritis in a late-onset rheumatoid arthritis (LORA) patient. *Ocul Immunol Inflamm.* 2007;15:33-36.
- Patel SJ, Lundy DC. Ocular manifestations of autoimmune disease. *Am Fam Physician.* 2002;66:991-998.
- Atchia II, Kidd CE, Bell RW. Rheumatoid arthritis-associated necrotizing scleritis and peripheral ulcerative keratitis treated successfully with infliximab. *J Clin Rheumatol.* 2006;12:291-293.
- Messmer EM, Foster CS. Vasculitic peripheral ulcerative keratitis. *Surv Ophthalmol.* 1999;43:379-396.
- Piper H, Douglas KM, Treharne GJ, Mitton DL, Haider S, Kitas GD. Prevalence and predictors of ocular manifestations of RA: is there a need for routine screening? *Musculoskeletal Care.* 2007;5:102-117.
- Chhablani J, Wong IY, Kozak I. Choroidal imaging: A review. *Saudi J Ophthalmol.* 2014;28:123-128.
- Lim SH. Clinical applications of anterior segment optical coherence tomography. *J Ophthalmol.* 2015;2015:605729.
- Turesson C, O'Fallon WM, Crowson CS, Gabriel SE, Matteson EL. Extra-articular disease manifestations in rheumatoid arthritis: incidence trends and risk factors over 46 years. *Ann Rheum Dis.* 2003;62:722-727.
- Zlatanović G, Veselinović D, Cekić S, Zivković M, Dordević-Jocić J, Zlatanović M. Ocular manifestation of rheumatoid arthritis-different forms and frequency. *Bosn J Basic Med Sci.* 2010;10:323-327.
- Feldmann M, Brennan FM, Maini RN. Rheumatoid arthritis. *Cell.* 1996;85:307-310.
- Squirrell DM, Winfield J, Amos RS. Peripheral ulcerative keratitis 'corneal melt' and rheumatoid arthritis: a case series. *Rheumatology (Oxford).* 1999;38:1245-1248.
- Prada J, Noelle B, Baatz H, Hartmann C, Pleyer U. Tumour necrosis factor alpha and interleukin 6 gene expression in keratocytes from patients with rheumatoid corneal ulcerations. *Br J Ophthalmol.* 2003;87:548-550.
- Villani E, Galimberti D, Viola F, Mapelli C, Del Papa N, Ratiglia R. Corneal involvement in rheumatoid arthritis: an in vivo confocal study. *Invest Ophthalmol Vis Sci.* 2008;49:560-564.
- Cingü AK, Cınar Y, Türkcü FM, Sahin M, Kaya S, Bozkurt M, Sahin A, Yüksel H, Ari S, Çaça I. Evaluation of corneal parameters with sheimpflug imaging in patients with rheumatoid arthritis. *Ocul Immunol Inflamm.* 2013;21:360-365.
- Taş M, Öner V, Özkaya E, Durmuş M. Evaluation of corneal biomechanical properties in patients with rheumatoid arthritis: a study by ocular response analyzer. *Ocul Immunol Inflamm.* 2014;22:224-227.
- Gunes A, Inal EE, Tok L, Tok O. Evaluation of central and peripheral corneal thicknesses in patients with rheumatoid arthritis. *Arq Bras Oftalmol.* 2015;78:236-240.
- McGavin DD, Williamson J, Forrester JV, Foulds WS, Buchanan WW, Dick WC, Lee P, MacSween RN, Whaley K. Episcleritis and scleritis. A study of their clinical manifestations and association with rheumatoid arthritis. *Br J Ophthalmol.* 1976;60:192-226.
- Kim M, Kim H, Kwon HJ, Kim SS, Koh HJ, Lee SC. Choroidal thickness in Behcet's uveitis: an enhanced depth imaging-optical coherence tomography and its association with angiographic changes. *Invest Ophthalmol Vis Sci.* 2013;54:6033-6039.
- Taban M, Sharma S, Williams DR, Waheed N, Kaiser PK. Comparing retinal thickness measurements using automated fast macular thickness map versus six-radial line scans with manual measurements. *Ophthalmology.* 2009;116:964-970.
- Heussen FM, Ouyang Y, McDonnell EC, Narala R, Ruiz-Garcia H, Walsh AC, Sadda SR. Comparison of manually corrected retinal thickness measurements from multiple spectral-domain optical coherence tomography instruments. *Br J Ophthalmol.* 2012;96:380-385.
- Okhravi N, Oduduwa B, McCluskey P, Lightman S. Scleritis. *Surv Ophthalmol.* 2005;50:351-363.
- Bernaer W, Büchi ER, Daicker B. Immunopathological findings in posterior scleritis. *Int Ophthalmol.* 1994-1995;18:229-231.
- Van Vollenhoven RE. Sex differences in rheumatoid arthritis: more than meets the eye. *BMC Med.* 2009;7:12.
- Nowinska AK, Teper SJ, Janiszewska DA, Lyssek-Boron A, Dobrowolski D, Koprowski R, Wylegala E. Comparative Study of Anterior Eye Segment Measurements with Spectral Swept-Source and Time-Domain Optical Coherence Tomography in Eyes with Corneal Dystrophies. *Biomed Res Int.* 2015;2015:805367.
- Khaja WA, Grover S, Kelmenson AT, Ferguson LR, Sambhav K, Chalam KV. Comparison of central corneal thickness: ultrasound pachymetry versus slit-lamp optical coherence tomography, specular microscopy, and Orbscan. *Clin Ophthalmol.* 2015;9:1065-1070.