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Corneal Structure and Biomechanics in Collagen Vascular Diseases

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ABSTRACT

Purpose: The purpose of this study was to evaluate corneal biomechanics and structure in asymptomatic individuals with Collagen Vascular Diseases (CVD), and compare with an age--matched control group.
Methods: In this prospective study 23 patients with the diagnosis of CVD (46 eyes) and 17 healthy age and gender-matched controls (34 eyes) underwent Ocular Response Analyzer and Specular Microscopy measurements. CH and CRF were recorded for each eye using the ORA, pachymetry and endothelial cell count were measured through Specular Microscopy.
Results: Mean CH was 10.1 +/- 1.3 mmHg in the study group and 10.0 +/- 1.2 mmHg in the control group. Mean CRF was 10.2 +/- 1.5 and 9.9 +/- 2.5 mmHg in the study and control groups respectively. These differences weren't statistically significant (p=0,75 and p=0,47 respectively). CH was significantly higher in patients treated with hydroxychloroquine (10.4) compared with those who had no treatment (9.4) (p=0.006). Likewise the average CH was significantly lower in patients with five or more years of disease 9.6 vs 10.7 mmHg (p=0.01).
Conclusions: Our results suggest no difference in the biomechanical properties of the cornea of individuals with CVD and a normal control population. However, there seems to be an inverse association between time since diagnosis and the value of CH. Additionally, there seems to be a relationship between the value of CH and treatment with hydroxychloroquine. Further studies are needed to help clarify the impact of CVD on corneal biomechanics, and possible implications on the risk of glaucoma and evaluation for refractive surgery.

Key-words
Corneal Hysteresis; Corneal Resistance Factor; Collagen Vascular Diseases; Ocular Response Analyzer.

INTRODUCTION

Collagen Vascular Diseases (CVD) are a heterogeneous group of autoimmune diseases of unknown etiology that affect connective tissue and small vessels. They include Rheumatoid Arthritis; Ankylosing Spondylitis; Systemic Lupus Erythematosus; Progressive Systemic Sclerosis; Wegener´s Granulomatosis; Dermatomyositis; Sjögren's Syndrome; Mixed Connective Tissue Disease; Polyarteritis Nodosa and Polymyositis[1].

CVD have well-known ocular associations that may be the presenting feature of the disease, or occur later as complications during the course of the illness. Ocular manifestations include: *keratoconjunctivitis sicca*, filamentary

or interstitial keratitis, peripheral ulcerative keratitis; corneal oedema or stromal fibrosis; endothelitis; (epi) scleritis, uveitis, retinal vasculitis, retinopathy, choroidopathy and optic neuritis[2]. Nevertheless these patients may have ultrastructural collagen anomalies even without clinical signs and symptoms of disease. Weather these changes give them further susceptibility or not remains a question.

The corneal stroma is responsible for the mechanical and refractive properties of the cornea. The anterior part of the corneal stroma is thought to be responsible for corneal shape and stability having a higher water content[3]. The posterior part is thought to be richer in collagen fibrils that need to have a closely packed and regular organization in order to maintain corneal transparency. Changes in the properties of corneal stroma occur with advancing age, corneal pathology, systemic diseases, and altered hydration, in which a loss of stromal lamellae organization modifies the corneal biomechanical properties[4]. Given the role of corneal connective tissue in corneal structure, the authors hypothesize that CVD could have an impact in the biomechanical and viscoelastic properties of this tissue. In this way we evaluated the structure and biomechanics of the cornea of individuals with CVD and compared them with a healthy age/gender-matched control group.

Corneal biomechanical evaluation may be useful for preoperative screening of refractive surgery candidates that do not have any ocular signs or symptoms of ocular disease, but still have a collagen vascular disorder. It may also be valuable in avoiding misinterpretation of the intraocular pressure (IOP)[4, 5, 6] and may even proof to be a window for *in vivo* screening of connective tissue damage in the body.

The Ocular Response Analyzer (ORA®, Reichert Inc., Depew, NY) is a non-contact tonometer for measuring *in vivo* the viscous and elastic properties of the cornea. It measures the IOP, corneal hysteresis (CH), corneal resistance factor (CRF) and corrected IOP for corneal biomechanics. CH is calculated as the difference between the two pressure values at two applanation processes, relates with corneal resistance, and represents the combined effect of corneal thickness, rigidity, hydration, and possibly other factors[3]. CRF is calculated as a linear function of the two applanation pressures, correlates with CH, but is more heavily weighted by corneal elasticity[7]. The ORA has a good reproducibility of corneal viscoelastic properties in a normal eye particularly for CRF (5.2 + / - 5.9%) and CH (7.3 + / - 8.6%)[8].

Specular Microscopy (Topcon Specular SP-2000 P®, Tokyo, Japan) is able to capture the image of the endothelial cells and calculate cornea´s thickness by a unique method that does not require touching the cornea. This patented procedure eliminates the risk of transmitting infectious disease and reduces potential physical injury to the eye. Patient comfort and cooperation is increased allowing examination time to be greatly reduced. It has an auto alignment and auto capture system.

MATERIAL AND METHODS

This was a prospective, cross-sectional study performed at Dr. Gama Pinto Institute of Ophthalmology in collaboration Santa Maria´s Hospital, university-based tertiary centers in Lisbon, Portugal. The study was approved by the Ethics Committee of the Dr. Gama Pinto Institute of Ophthalmology and followed the principles of the Declaration of Helsinki. Written informed consent was obtained form every patient.

Patients were evaluated from January until July 2012.

The study group was composed of 23 patients with the diagnosis of a Collagen Vascular Disease referred to us from Autoimmune Diseases Department in Santa Maria´s Hospital. The control group was composed of 17 healthy patients in whom CVD and any ocular pathology were excluded. Both eyes from patients in the study and control group were analyzed. All patients were over 18 years of age.

For correlation analysis we divided the study group into two subgroups regarding treatment or not with hydroxychloroquine (Plaquinol® BioSaude, Portugal) and again regarding duration of disease higher or equal to 5 years or lower than 5 years.

We excluded from this study patients with *Diabetes mellitus*; previous intra-ocular surgery; *major* ocular trauma; previous refractive surgery or corneal *crosslinking*; corneal ectasia; active keratitis; corneal dystrophy, degeneration or vascularization; amiodarone medication; anterior segment morphologic anomaly and an IOP > 21 mmHg. Patients under any topical medication other than artificial tears were also excluded from the study.

Clinical examination included best corrected visual acuity using a Snellen chart; slit-lamp examination of the anterior segment, indirect ophthalmoscopy under dilation, CH and CRF measurement using the (Ocular Response Analyzer (ORA®, Reichert Inc., Depew, NY); pachymetry (central corneal thickness) and endothelial cell count using Specular Microscopy (Topcon Specular SP-2000 P®, Japan).

Four good-quality ORA measurements were performed in all eyes by a single experienced physician, with the patient sitting in a chair, in the same room and in the same time schedule between 2 and 4 pm. Mean values from the 4 measurements were used for each parameter. Specular

microscopy was performed by the same physician always 30 minutes to 1 hour after ORA measurements. Neither exam involved direct ocular contact. For endothelial cell count 30 cells were manually chosen from the corneal mosaic (obtained from specular microscopy) to access endothelial cell count by the device´s software.

The statistical tests were performed using SPSS (SPSS Inc., Chicago, IL, USA) version 16. The normality of the data was confirmed using the Kolmogorov-Smirnov test (p>0,05). Student´s t-test was used for comparison of means, Pearson and Spearmen´s correlation was used to examine the relationships among the measured variables. A p value of <0,05 was considered statistically significant.

RESULTS

The demographic characteristics of the two groups are shown in table 1. Mean age in the study group was 53,5 +/- 11,7 years and 47,9 +/- 15,2 years in the control group (p = 0,20). The female:male ratio was 21 F: 2 M in the study group and 14 F: 3 M in the control group. There were no statistically significant differences between the two groups with regard to age and sex distribution. Mean duration of disease since diagnosis was 7,4 +/- 6,7 years.

Mean CH was 10,1 +/- 1,3 mmHg in the study group and 10,0 +/- 1,2 mmHg in the control group (p=0,75). Mean CRF was 10,2 +/- 1,5 mmHg in the study group and 9,9 +/- 2,5 mmHg in the control group (p=0,47). These differences weren´t statistically significant (see Table 2).

Table 1 | Demographic characteristics of patients.

Variable	Control group	Study group	P-value
Eyes (N)	34	46	
Female	14	21	
Male	3	2	
Age - years (Mean+/- SD)	47,9+/- 15,2	53,5 +/- 11,7	0,20*
Range	(28 – 66)	(30 – 71)	
SLE		N = 6	
SS		N = 2	
RA		N = 10	
AS		N = 2	
Behçet		N = 1	
MCTD		N = 2	

SLE - Systemic Lupus Erythematosus; SS – Primary Sjögren's Syndrome; RA - Rheumatoid Arthritis; AS - Ankylosing Spondylitis; MCTD - Mixed Connective Tissue Disease;
*Independent samples t-test. P – values significant at <0,05

Table 2 | Corneal biomechanical parameters in both groups.

Variable	Control group	Study group	P-value
CH, mmHg (Mean +/- SD)	10,0 +/- 1,2	10,1 +/- 1,3	0,75
Range	(8,0 – 11,9)	(7,3 – 12,4)	
CRF (Mean +/- SD)	9,9 +/- 2,5	10,2 +/- 1,5	0,47
Range	(7,2 – 15,1)	(6,8 – 12,7)	

P – values significant at <0,05

Fifteen patients (30 eyes) did treatment with hydroxychloroquine and 8 patients (16 eyes) did not. Mean duration of treatment with hydroxychloroquine was 2,0 +/- 1,5 years, mean dose was 260 +/- 91 mg/day. Mean CH was 10,4 mmHg in the subgroup who did treatment with hydroxychloroquine vs 9,4 mmHg in the subgroup of patients with CVD who did not. This difference was statistically significant (p=0,006). Mean age was similar in both groups excluding this as a possible bias. Regarding CRF no association was found with hydroxychloroquine treatment (10,3 +/- 1,4 vs 10,1 +/- 1,6 mmHg p=0,532). Results are plotted in table 3.

Analyzing duration of disease and corneal biomechanical parameters we found a statistically significant difference between CH in patients who had a CVD for 5 or more years

Table 3 | Relationship between hydroxychloroquine and corneal biomechanical parameters.

	HCQ	Not on HCQ	P-value
Eyes (N)	30	16	
Age (years)	51,7	56,8	0,34
CH, mmHg (Mean +/- SD)	10,4 +/- 1,3	9,4 +/- 1,0	0,006
Range	(6,9 – 12,4)	(8,2 – 10,6)	
CRF (Mean +/- SD	10,3 +/- 1,4	10,1 +/- 1,6	0,53
Range	(7,0 – 12,7)	(6,8 – 11,8)	

HCQ – hydroxychloroquine
P – values significant at <0,05

Table 4 | Duration of disease and corneal biomechanical parameters.

	CVD < 5 years	CVD ≥ 5 years	P-value
Eyes (N)	22	24	
Age (years)	49,6 +/- 12,1	57 +/- 10,7	0,136
CH, mmHg (Mean+/- SD)	10,6 +/- 1,4	9,7 +/- 1,0	0,015
Range	(6,9 – 12,4)	(8,0 – 11,6)	
CRF (Mean +/- SD)	10,6 +/- 1,5	9,9 +/- 1,4	0,086
Range	(7,0 – 12,7)	(6,8 – 11,8)	

P – values significant at <0,05

against those who had the disease for less than 5 years (CH – 9,7 +/- 1,0 vs 10,6 +/- 1,4 mmHg; p=0,015). Spearman´s correlation factor confirmed this inverse correlation (ρ=-0,330). Again regarding CRF no association was found with duration of disease (9,9 +/- 1,4 mmHg vs 10,6 +/- 1,5 mmHg p=0,086). Results are plotted in table 4.

After this we studied the relationship between age and CH and we found out a statistically significant correlation between age and CH in CVD (p=0,030 r= -0,320). This association was not found on the control group (p=0,677 r=0,074) . Regarding CRF no association was found with age.

Mean CCT was 535,3 +/- 30,9 µm in the study group and 539,6 +/- 57,6 µm in the control group with no significant difference between them (p=0,68).

Mean endothelial cell count in the study group was 2601 +/- 681 cells/mm^2 with no relation found with CH.

DISCUSSION

Corneal characteristics in Collagen Vascular Diseases are important in order to know how to deal with this kind of patients, especially when they are asymptomatic and have no visible ocular alterations. Many of these patients are young and may want to perform keratorefractive surgery. We need to be able to exclude with certainty clinical or subclinical keratoconus, as well as identify those who may have corneal post-operative complications like ectasia, melting or keratitis. On the other hand we need to know how to correctly access IOP measurements and glaucoma. Several studies have tried to characterize corneal biomechanic properties in this type of diseases, however controversy remains and results between different series have been conflicting. *Yazici et al*[4] reported lower CH and CRF values in 30 patients with Systemic Lupus Erythematosus compared with age--matched controls. He also found no correlation between duration of disease, age and axial length with CH and CRF in both groups. *Emre et al*[9] investigated corneal biomechanical properties in 29 patients with Scleroderma and found mean CRF and IOPg values higher in these patients than those of age-matched healthy controls. *Prata et al*[6] reported lower CH and IOP values in 11 patients with Rheumatoid Arthritis than age-matched controls.

In our study we found no significant differences in the biomechanical properties of the cornea of CVD individuals without ocular signs and symptoms of disease, and a normal age-matched control population. CH and CRF didn´t differ significantly between both groups.

However we found a significant inverse association between age and CH in CVD group and not in the healthy control group. We also found a significant inverse association between duration of disease and CH. Patients with more than 5 years of disease appear to have lower values of CH than those who have the disease for less years. This didn´t confirm regarding CRF. In face of these results it is possible that with advancing age, the anomalous collagen tissue of these patients may lead to changes in corneal rigidity and hydration.

Interestingly we also found a direct correlation between CH and treatment with hydroxychloroquine. The mean treatment time was 2,0 years with a mean dose of 260 mg. It is well known that antimalarial drugs are beneficial in CVD[10], relieving symptoms and diminishing inflammation. Maybe patients with underlying disease better controlled remain with higher CH than patients who do not.

In conclusion, this study was the first to demonstrate a decrease in CH with the duration of the CVD, as well as a relative improvement in this parameter in those patients treated with hydroxychloroquine. This finding suggests the existence of asymptomatic ultra structural corneal changes in these patients. The impact of these biomechanical changes in IOP measurement and corneal refractive surgery, as well as the potential protective effect of hydroxychloroquine needs further evaluation in future studies. Treatment with hydroxychloroquine may be beneficial in stabilizing corneal viscoelastic properties but one must never not forget screening for retinal toxicity which, even though very rare, seems to be the major side effect of this drug.

Understanding corneal viscoelastic properties of these patients may be important in evaluation for refractive surgery in asymptomatic patients, and may eventually become a weapon for in vivo screening of connective tissue body damage in these patients.

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