

Optic Nerve Head Elasticity and Corneal Biomechanics in Patients with Optical Disc Drusen and Optic Disc Edema

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Research Article

Keywords: Optic disc drusen, Optic disc edema, Ultrasound elastography, Optic nerve head biomechanics, Corneal biomechanics

Posted Date: April 26th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-439912/v1>

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Abstract

Purpose: The purpose of the study is to evaluate the efficacy of ultrasound elastography (USE) in differentiating optic disc drusen (ODD) from optic disc edema (ODE) and to investigate the relationship between corneal biomechanics and optic nerve elasticity.

Methods: This prospective, clinical study included 28 eyes of 16 ODD patients (Group 1), 23 eyes of 18 ODE patients (Group 2) and 30 eyes of 15 healthy controls (Group 3). Best corrected distance visual acuity (BDVA), corneal hysteresis (CH), corneal resistance factor (CRF), corneal-compensated intraocular pressure (IOPcc), Goldmann-correlated IOP (IOPg) and optic nerve head (ONH)-elasticity were measured.

Results: The mean BDVA value was significantly lower in Group 2 compared to Groups 1 and 3 ($p < 0.001$), there was no significant difference between Groups 1 and 3 ($p = 0.089$). The mean intraconal fat to ONH ratio was significantly higher in Group 1 compared to Group 2 ($p = 0.008$) and 3 ($p = 0.002$), there was no significant difference between Group 2 and 3 ($p = 0.182$). The receiver operating characteristic curve areas for ONH-elasticity in differentiating group 1 and group 2 was 0.728 ($p = 0.008$) with 80% sensitivity and 60% specificity when the cut-off point was set at 2.29. Corneal biomechanics (CH, CRF, IOPcc, IOPg) were not different between the three groups ($p > 0.05$), however there was a significant correlation between corneal and ONH biomechanics in drusen group ($p < 0.05$).

Conclusion: The evaluation of the ONH with USE seems to provide useful data in differentiating ODD from ODE. Significant correlation was revealed between corneal and ONH biomechanics in drusen group.

Introduction

Optic disc drusen (ODD) is a congenital, benign optic disc anomaly caused by impairment of axoplasmic flow in the narrow scleral channel and consequent accumulation of pathological calcification debris in the hyaline structure of the optic disc [1]. Its prevalence ranged from 3.4–24% in clinical trials, while it was found to be 1% and 2.4% in histological examinations [2, 3]. ODD is more commonly seen in women and its bilaterality rate is around 75% [4, 5].

According to previous reports, ODD may be associated with other ocular diseases or may mimic them, however the most important differential diagnosis of bilateral ODD is optic disc edema (ODE), which is more associated with increased intracranial pressure or an optic neuropathy and requires prompt treatment [6–8]. Imaging methods play an important role in the differential diagnosis of these two pathologies (ODD and ODE) that have different clinical findings and interventions [7]. Superficially located ODDs are easily diagnosed during fundus examination while to detect the buried ones, additional imaging methods such as B-scan ultrasonography (USG), fundus fluorescein angiography (FFA), computed tomography (CT) and fundus autofluorescence (FOF) are needed. In recent years, with the development of spectral domain optical coherence tomography (SD-OCT), the optic nerve head (ONH) has begun to be examined real time (with reproducible images) and early changes in the retinal nerve

fiber layer could be detected more reliably. In a previous study of our group, SD-OCT has shown to be effective even in the differential diagnosis of ODD and ODE [9].

Other than these mostly used imaging techniques, in recent years, elastography has been introduced in ophthalmology as a new sonographic technique and started to use in the evaluation of orbital diseases. Up to date, studies have investigated its effectiveness in the evaluation of ONH in patients with multiple sclerosis, Behcet's disease, primary open angle glaucoma (POAG), non-arteritic anterior ischaemic optic neuropathy (NAION) and optic neuritis [10–14]. However, no study has evaluated its usefulness in ODD or in the differential diagnosis of ODD with other conditions such as ODE yet.

On the other hand, evaluation of corneal biomechanics and its association with other parts of the eye has begun to give significant outcomes. Association of corneal biomechanics with the ONH biomechanics has also been investigated recently using ultrasound elastography (USE) in patients with NAION and a positive correlation was found between corneal rigidity and optic nerve rigidity [13].

In this current study, we aimed to use USE in the evaluation of ODD and differential diagnosis of ODD with ODE. In addition, we aimed to investigate the corneal biomechanics of our study groups to evaluate the relationship between corneal biomechanics and ONH-elasticity.

Materials And Methods

Patient Population

This prospective, comparative clinical study included patients diagnosed with ODD and ODE in the Neuro-ophthalmology Department of Yildirim Beyazit University Ankara, Turkey and healthy controls. Prior to the study, an institutional review board approval was obtained and adhered to the tenets of the Declaration of Helsinki. Detailed written informed consent was obtained from all patients and control subjects.

Inclusion and Exclusion Criteria

Patients who were diagnosed with definitive ODD and ODE using other imaging techniques, laboratory tests, and neurology consultation were included in this study. Patients with a history of ocular surgery, serious coexistent ocular disease, glaucoma, cataract, diabetes, retinal disease, and other systemic diseases affecting the eye were not included to the study. Healthy controls were included from the subjects who had no ocular or systemic disease diagnosis.

Ophthalmologic Examination

All patients underwent detailed ophthalmologic examination including best-corrected distance visual acuity (BDVA), Ishihara color blindness test, pupillary light reflex, intraocular pressure measurement with Goldmann applanation tonometer, biomicroscopic anterior segment and fundus examination. Besides, corneal hysteresis (CH), corneal resistance factor (CRF), corneal-compensated intraocular pressure

(IOPcc) and Goldmann-correlated IOP (IOPg) were measured using ocular response analyzer (ORA, Reichert, USA), and ONH-elasticity evaluation was assessed using USE.

Ultrasound Elastography

Freehand USE examination was performed with a high frequency linear probe (12– 17 MHz) on an Aplio 500 ultrasound machine (Toshiba Medical Systems, Co, Ltd, Otawara, Japan) by the same radiologist (OU) experienced on B-scan USG and elastography. After evaluation of the orbit with conventional USG, the patient was placed in the supine position, the USG probe was placed on the patient's lids, the orbit was compressed with the probe by applying a slight vertical pressure and elastography examination was performed (with the existing elasto-software). B-scan images of the orbit were displayed in the right half of the monitor and elastographic images in the left half of the monitor. The elasticity images were produced by continuously moving the probe to obtain compression and relaxation waveforms. After 10 to 12 compression and relaxation cycles, the elastographic examination was terminated and strain rate measurements were obtained. Compression and relaxation waveforms were displayed on the elastographic display, above and below the wave scale baseline. Repeated measurements were taken by performing a very light compression / release 3 times at 1 to 2 second intervals at a relatively slow rate. Compression / release is considered to be appropriate when the velocity profile displayed at the bottom of the screen is nearly sinusoidal and the release (lower side) is considered to be closer to the actual strain value than the compression (upper side). Although the color display was provided immediately after the initial vibration (after 1–2 seconds), the image continued to be displayed until the color in the displayed area was completely stable to obtain reliable measurement results. Strain images were obtained according to the color scale based on the degree of stress (blue is hard tissue, green is medium hardness and red is soft). The strain ratios (fat-lesion- ONH ratio) of all groups were recorded. Figure 1 shows the gray-scale ultrasonography images and the related strain elastography images of ONH versus intraconal fat (IF) in patients with ODD and ODE and healthy controls.

Statistical Analysis

SPSS Statistics 22.0 (SPSS, Inc, Chicago, IL) was used to calculate means and standard deviations for all variables. The Kolmogorov–Smirnov test was used to analyze the normal distribution of data. The male-to-female ratio of the groups was compared using the Chi-square test. CH, CRF, USE and RNFL measurements were analyzed using the Mann–Whitney U test. Spearman's rho correlation tests were calculated to assess the relationship of the optic nerve elasticity with CH and CRF. Receiver-operating characteristic (ROC) curves were used to determine the predictive accuracy of the optic nerve elasticity as described by the area under the curve and to calculate the sensitivity and specificity of the optic nerve elasticity for a determined cut-off point. P-values less than 0.05 were considered as statistically significant.

Results

Twenty-eight eyes of 16 ODD patients (Group 1), 23 eyes of 18 ODE patients (Group 2), and 30 eyes of 15 healthy controls (Group 3) were included in this study. Patient demographics were shown in Table 1. Mean BDVA values were 0.00 ± 0.03 , 0.15 ± 0.56 and 0.00 ± 0.00 (LogMAR) in Group 1, Group 2, and Group 3, respectively. There was no statistically significant difference between Groups 1 and 3 ($p = 0.089$), while; there was a significant difference between Groups 2 and 3 ($p < 0.001$).

Table 1
Patient demographics

	Group 1	Group 2	Group 3	p^*	p^{**}	p^{***}
Age (Years)	30.48 ± 15.9 (12–65)	37.95 ± 15.0 (17–62)	31.73 ± 8.2 (14–42)	0.063	0.258	0.061
Gender (Female/Male)	11 (%69) / 5 (%31)	11 (%61) / 7 (%39)	11 (%63) / 4 (%27)	0.410	0.252	0.432
*Comparisons between Group 1 and 2; **Comparisons between Group 2 and 3; ***Comparisons between Group 1 and 3.						

Comparisons of USE outcomes between groups were shown in Table 2. The mean IF to ONH ratio was significantly higher in Group 1 compared to Group 2 ($p = 0.008$) and 3 ($p = 0.002$) and there was no significant difference with respect to ONH-elasticity between Group 2 and 3 ($p = 0.182$).

Table 2
Comparisons of USE outcomes between groups

	Group 1	Group 2	Group 3	p^*	p^{**}	p^{***}
IF/ONH	3.2 ± 1.3	2.2 ± 1.1	1.4 ± 1.3	0.008	0.182	0.002
Elasticity	(1.2–6.4)	(0.9–5.9)	(0.1–4.8)			
IF = Intraconal Fat; ONH = Optic Nerve Head. *Comparisons between Group 1 and 2; **Comparisons between Group 2 and 3; ***Comparisons between Group 1 and 3.						

While differentiating groups 1 and 2, the ROC curve areas were calculated for ONH- elasticity. The ROC curve under area for ONH-elasticity was 0.728 and it was statistically significant ($p = 0.008$). When the cut-off point was set at 2.29, 80% sensitivity and 60% specificity were obtained.

Table 3 shows the comparison of corneal biomechanics between groups. There was no significant difference between three groups with respect to CH, CRF, IOPcc and IOPg results ($p > 0.05$). Besides, as shown in Table 4, we performed a correlation analysis between corneal biomechanics and ONH elasticity and found a negative correlation between CH and ONH biomechanics and a positive correlation between IOPcc, IOPg and ONH biomechanics only in drusen group ($p < 0.05$).

Table 3
Comparison of corneal biomechanics between groups

	Group 1	Group 2	Group 3	<i>p</i> *	<i>p</i> **	<i>p</i> ***
CH (mmHg)	10.1 ± 0.8 (9.1–12.5)	10.2 ± 1.1 (9.1–12.5)	9.8 ± 1.7 (5.3–12.2)	0.502	0.514	0.158
CRF (mmHg)	10.4 ± 1.1 (7.8–13.1)	10.1 ± 1.1 (7.6–11.8)	10.2 ± 1.7 (6.2–13.6)	0.869	0.975	0.648
IOPcc (mmHg)	15.2 ± 2.6 (9.1–20.1)	15.7 ± 1.8 (12–20.6)	16.6 ± 2.8 (13–21.9)	0.502	0.162	0.072
IOPg (mmHg)	14.8 ± 2.8 (7.3–21)	15.0 ± 1.7 (10.6–18)	16.06 ± 3.3 (10.9–20)	0.834	0.074	0.097
CH = Corneal Hysteresis; CRF = Corneal Resistance Factor; IOPcc = Corneal Compensated Intraocular Pressure; IOPg = Goldmann correlated Intraocular Pressure. *Comparisons between Group 1 and 2; **Comparisons between Group 2 and 3; ***Comparisons between Group 1 and 3.						

Table 4
Correlation analysis between corneal biomechanic parameters and ONH elasticity

	Group 1		Group 2		Group 3	
	ONH Elasticity		ONH Elasticity		ONH Elasticity	
	<i>r</i>	<i>p</i>	<i>r</i>	<i>p</i>	<i>r</i>	<i>p</i>
CH (mmHg)	-0,425	0,050	0.174	0.436	0.376	0.064
CRF (mmHg)	0,069	0.767	0.198	0.378	0.216	0.300
IOPcc (mmHg)	0.553	0.009	-0.033	0.886	-0.153	0.466
IOPg (mmHg)	0.429	0.050	0.102	0.653	-0.077	0.716
ONH = Optic Nerve Head; CH = Corneal Hysteresis; CRF = Corneal Resistance Factor; IOPcc = Corneal Compensated Intraocular Pressure; IOPg = Goldmann correlated Intraocular Pressure						

Discussion

Ultrasound elastography is a noninvasive imaging method that evaluates the mechanical and elastic properties of soft tissues by estimating the strain modules from radiofrequency signals during externally applied compression–relaxation cycles [15]. This method has been used to measure elasticity and stiffness of the tissues to differentiate for instance the tumor tissue from inflammation and normal tissue. Evaluation of some solid organs such as thyroid [16], prostate [17], liver [18], breast [19] and cervix [20] have been performed with this method for many years it was first found in 2010 to be useful in ocular and periocular tissues [21] as well.

With the introduction of USE into ophthalmology, a limited number of preclinical and clinical studies have been conducted to assess its usefulness. In 2014, Detorakis et al. revealed that the USE was useful in detecting in vivo rigidity changes in the anterior segment in an experimental study, which was conducted in a rabbit eye model to evaluate lens, ciliary body, and total ocular rigidity changes [22]. In a clinical study, Unal et al. investigated the effects of ocular rigidity changes on optic nerve in patients with POAG using USE method and found a stiffer ONH in eyes with POAG when compared with non-glaucomatous control eyes [12]. Then, the evaluation of the ONH by using USE became more common and has been applied in some other optic nerve related diseases such as multiple sclerosis [10], Behçet's disease [11], non-arterial anterior ischemic optic neuropathy [13], and optic neuritis [14]. In all these diseases, the elastography findings of the ONH were significantly different from the healthy volunteers. With the light of this significant information, we aimed to utilize USE in the present study in the evaluation of ODD and in the differential diagnosis of ODD with ODE, which has been still considered as a challenging condition in clinical practice.

Since ODD is known as calcified hyaline body located within the ONH, it can be expected that its' stiffness is higher than other tissues around [1]. With this hypothesis, in this study, we chose the orbital fat tissue as a reference, which is softer than optic nerve, and evaluated ONH-elasticity in proportion to this tissue. According to our results, the ONH- elasticity was significantly lower in patients with ODD compared to patients with ODE and healthy controls. There was no statistically significant difference with respect ONH-elasticity between patients with ODE and healthy controls. In addition, we performed a ROC analysis to evaluate how effective the ONH-elasticity could be in the differential diagnosis of ODD and ODE. When the cut-off point for IF/ONH ratio was set at 2.29, 80% sensitivity and 60% specificity were obtained. The area under curve (AUC) value of ONH-elasticity was 0.728 with a significant difference. With this result, we could state that ONH-elasticity measurement seems to be a good predictor in the differential diagnosis of ODD and ODE and it can be used in daily clinic, since the differentiation of these two diagnoses is quite challenging and the diagnostic tools are still limited.

On the other hand, a recent study investigated the relationship between the cornea and the optic nerve in terms of biomechanical properties using USE, found a positive correlation between corneal rigidity and optic nerve rigidity in patients with NAION [13]. In the light of these results, we wanted to investigate the corneal biomechanics (by evaluating CH, CRF, IOPcc and IOPG values) in our study groups and their relationship with optic nerve elasticity. According to our results, there was no significant difference between groups with respect to corneal biomechanics, however there was a significant correlation

between corneal and ONH biomechanics only in drusen group (negative correlation between CH and ONH biomechanics and positive correlation between IOPcc, IOPg and ONH biomechanics). There was no correlation between CRF and ONH biomechanics in any group, however CRF was previously shown to be relatively independent of IOP, therefore our results are consistent with the literature.

Our study has some limitations. We used strain elastography in our study since it was the only tool we had in our hospital, however it has some limitations for application in ocular and periocular tissues (the compression effects in deeper orbital layers may not be adequate). Besides, the examination area was small and tightly organized and obtaining a high-resolution image was not easy, therefore, we had to repeat tests to get the best image. Despite these limitations, we believe that our study presents promising findings in support of the use of USE in differentiating ODE from ODD. As far as we know, this is the first study in the literature using USE in the evaluation of ODD and in the differential diagnosis of ODD with ODE.

In conclusion, USE seems to provide useful data in the evaluation of the ONH and in the differentiating ODD from ODE. Revealed significant correlation between corneal and ONH biomechanics also seems interesting, however further studies with larger population are needed to confirm these promising results.

Declarations

Funding: None

Conflict of Interest: No conflicting relationship exists for authors.

Availability of data and material: Available in case of need

Code availability: Not applicable

Ethics approval: Ethical approval obtained from Ankara Yildirim Beyazit University, Faculty of Medicine.

Consent to participate: Detailed written informed consent was obtained from all patients.

Consent for publication: Consent for publication was obtained

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Figures

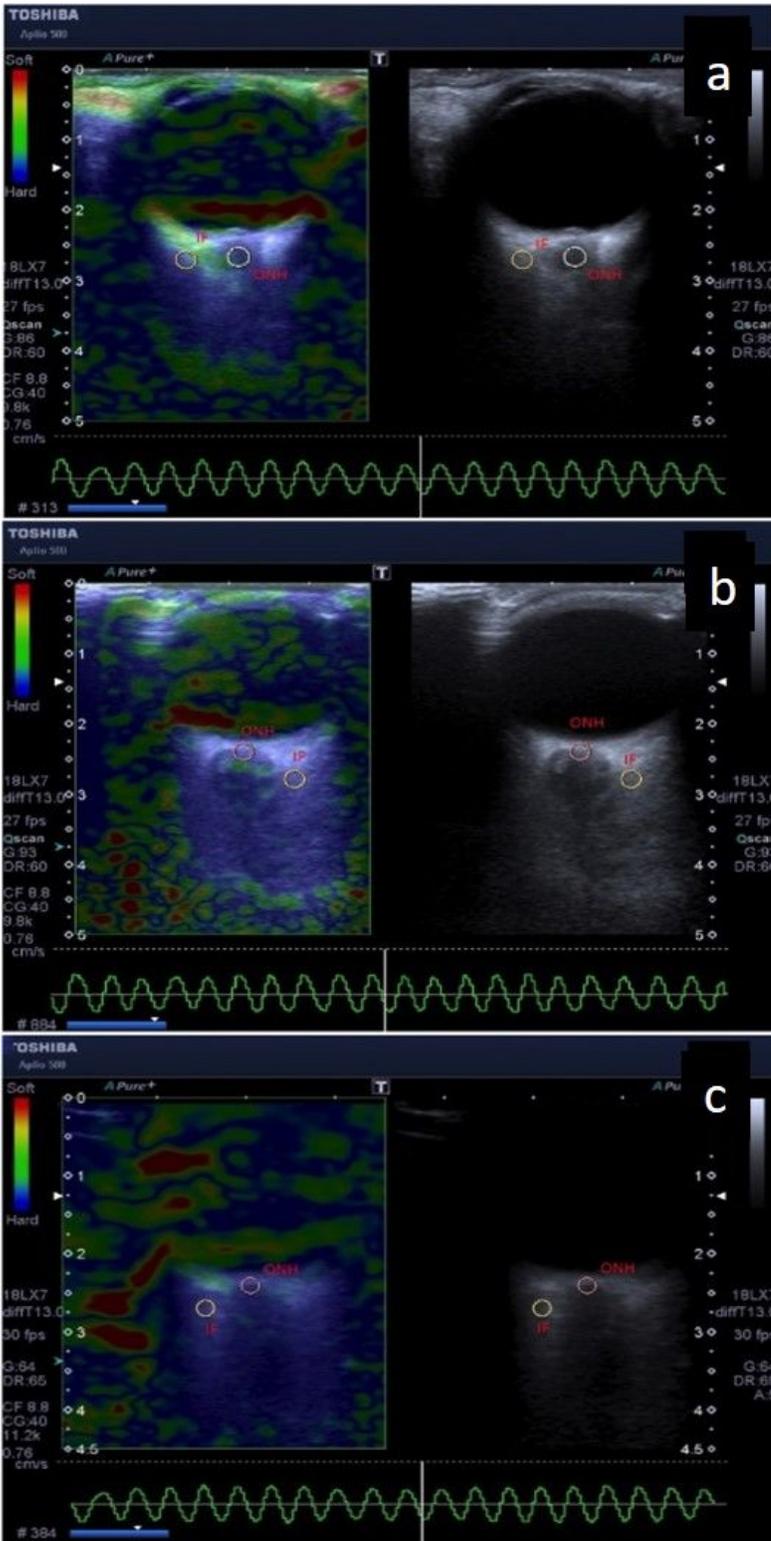


Figure 1

Gray-scale ultrasonography images and the related strain elastography images of optic nerve head versus intraconal fat. The circles show the places where the elastographic measurements were done. The pressure cycles show the strength of the repetitive sinusoidal compressions applied by the probe. a: Demonstrating a patient with optic disc drusen, b: Demonstrating a patient with optic disc edema, c: Demonstrating a healthy control. (ONH= Optic Nerve Head; IF= Intraconal Fat)