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ORIGINAL ARTICLE

Effect of Intravitreal Injection of Ranibizumab (Lucentis) on Corneal Biomechanics

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Abstract

Background: **Corneal biomechanics has become an interesting material for research and progress in modern ophthalmology due to its many uses. In the glaucoma field, biomechanically corrected IOP was measured. Also, in preoperative assessment in refractive surgery, KC and CXL.**

Corneal Visualization Scheimpflug Technology (Corvis ST) is a dynamic Scheimpflug technology measure that details the cornea's biomechanical reaction to an air pulse. Intravitreal anti-VEGF treatment causes a decrease of VEGF levels and a shift of CTGF/VEGF balance in favor of CTGF which is present in various tissues such as cornea and sclera causing antifibrotic switch.

Aim: **To assess the effect of intravitreal injection of ranibizumab (Lucentis) on corneal biomechanics using Corvis ST.**

Patients and methods: **This is a prospective, interventional, and nonrandomized study includes 30 eyes of 30 patients. Before and 1 month after a 3-months treatment of IVI of ranibizumab, Corvis ST parameters were obtained.**

Results: **Of the study showed that IOP and bIOP have increased significantly after the injection (*P* value 0.03, 0.04, respectively). A significant decrease of CCT after injection was found (*P* value 0.044). Ambrósio relational thickness over the horizontal meridian (ARTh) showed a significant decrease which correlates with the significant decrease in Corvis Biomechanical Index (CBI) after injection, which means better corneal biomechanical response (*P* values were 0.003, 0.014, respectively).**

Conclusion: **In this study intravitreal Ranibizumab injection could change some Corvis ST parameters and other parameters are nonstatistically different. This suggests the assessment of corneal biomechanics using Corvis ST on a wide scale.**

Keywords: Corneal biomechanics, Corneal visualization scheimpflug technology, Intravitreal injection, Ranibizumab

1. Introduction

Nowadays, anti-VEGF plays an important and rising role in retinal vascular disorders. At first, it was created to decrease the tumor's vascular supply when systemic cancers are present. Anti-VEGF drugs (including ranibizumab) have been injected into the vitreous cavity for numerous disorders like proliferative diabetic retinopathy, age-related macular degeneration, cystoid macular edema, and retinal vein occlusion.[1]

Moreover, there is scant information about its systemic or local effects on the other tissues of the eye after intravitreal injection.[1]

It has been discovered that VEGF and connective tissue growth factor (CTGF) interact. By binding to the CTGF-VEGF protein, CTGF can prevent VEGF-induced angiogenesis[2] and VEGF can increase the production and expression of CTGF.[3]

Intravitreal anti-VEGF treatment causes a decrease in VEGF levels and a shift of CTGF/VEGF balance in the side of CTGF and causes antifibrotic switch. The same effect has been found in unwounded normal cornea which may lead to changes in corneal stiffness and biomechanics.[3]

The viscoelastic properties of the cornea make it an effective biological mechanotransducer of stress. Because of the complexity of viscoelastic behavior, a

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Table 1. Demographic data of patients under the study.

	No. = 30
Age (Y)	
Mean ± SD	59.60 ± 10.58
Range	25–72
Sex	
Females	9 (30.0 %)
Males	21 (70.0 %)
Affected eye	
Right	20 (66.7 %)
Left	10 (33.3 %)

tissue's response depends on the strain rate, which affects the deformation during the loading/unloading cycle.[4]

The scientific field of biomechanics of the cornea assesses the deformation and equilibrium of ocular tissue under any force.[5]

Corneal biomechanics has an avital role in post-refractive surgery monitoring, diagnosis, and characterization of ocular diseases such as assessment of candidates of corneal refractive surgery and ectasia.[6]

Moreover, Corneal biomechanics is important in glaucoma diagnosis and follow-up, especially in normal tension glaucoma.[7]

In vivo biomechanics of cornea can be studied by using Corvis ST which was placed on the global market. Nowadays, it is the second device, just behind the ORA (ocular response analyzer), which provides biomechanical parameters of the cornea.[5]

The noncontact tonometer Corvis ST (OCULUS-Wetzlar-Germany) employs a high-speed Scheimpflug camera to examine the biomechanical characteristics of the human cornea *in vivo*. It makes use of a very fast Scheimpflug camera, which captures 140 horizontal 8 mm frames in a time interval of 33 ms (4330 frames/s).[8]

The cornea first advances inward during the air pulse until it reaches the first applanation, at which point it shifts into a concavity phase. After then, the cornea moves outward and experiences a second applanation before returning to its initial position.[8]

During this movement, Corvis ST measures the dynamic corneal response (DCR) with various metrics. The DCR measures, applanation lengths (AL), deformation amplitude (DA), corneal velocities (CVel) measured in the time of inward and outward stages and radius of curvature at the

Table 2. Visual acuity, best corrected visual acuity and diagnosis of patients.

Before	No. = 30
UCVA	
Mean ± SD	1.54 ± 0.18
Range	1.3–1.78
BCVA	
Mean ± SD	1.54 ± 0.20
Range	1.18–1.78
Diagnosis	
CNV	13 (43.3 %)
CRVO	2 (6.7 %)
BRVO	7 (23.3 %)
DME	8 (26.7 %)

CNV, Corneal Non visual

Table 3. Corvis parameters results among the studied patients before injection.

Corvis before injection	No. = 30
APPL1 length (mm)	
Mean ± SD	2.34 ± 0.33
Range	1.86–2.86
APP1 velocity (m/s)	
Mean ± SD	0.14 ± 0.02
Range	0.1–0.17
APP2 length (mm)	
Mean ± SD	2.15 ± 0.47
Range	1.48–3.1
APP2 velocity (m/s)	
Mean ± SD	−0.25 ± 0.02
Range	−0.28 to −0.22
IOP (mmhg)	
Mean ± SD	15.98 ± 2.20
Range	13.5–20.5
Biop (mmhg)	
Mean ± SD	14.46 ± 1.72
Range	12.7–18.2
Peak distance at HC (mm)	
Mean ± SD	4.94 ± 0.67
Range	4.16–7.2
Radius of highest concavity (mm)	
Mean ± SD	7.70 ± 0.66
Range	6.31–9
DA (mm)	
Mean ± SD	1.05 ± 0.07
Range	0.94–1.19
DA ratio	
Mean ± SD	4.33 ± 0.47
Range	3.5–5.6
CCT (mm)	
Mean ± SD	558.93 ± 30.72
Range	508–607
Integrated radius	
Mean ± SD	7.48 ± 0.78
Range	6.1–9.5
THC MD (ms)	
Mean ± SD	17.10 ± 0.88
Range	14.8–18
SSI	
Mean ± SD	1.29 ± 0.18
Range	0.93–1.63
ARTh	
Mean ± SD	526.80 ± 103.17
Range	353–779.3
CBI	
Mean ± SD	0.22 ± 0.23
Range	0.02–0.89

IOP, Intra ocular Pressure; bIOP, basic Intra ocular Pressure

Table 4. Uncorrected visual acuity and best corrected visual acuity comparison before and after injection.

LogMar	Before injection	After injection	Difference	Test value[a]	*P*-value	Sig.
	No. = 30	No. = 30	Mean ± SE			
UCVA						
Mean ± SD	1.54 ± 0.18	1.33 ± 0.28	−0.22 ± 0.04	−5.301	0.000	HS
Range	1.3–1.78	1–1.78				
BCVA						
Mean ± SD	1.54 ± 0.20	1.06 ± 0.55	−0.47 ± 0.09	−5.291	0.000	HS
Range	1.18–1.78	−0.19–1.78				

[a] Paired *t*-test.

highest concavity (Curvature radius HC), and then calculating corneal thickness and IOP.[9]

The investigators incorporated newly found criteria to the Vinciguerra screening report. This display gives acorrelation of normality values and a biomechanically corrected IOP. It uses calibration factor to calculate the IOP depending on the pressure at the time of first applanation. It makes it possible to calculate Corvis Biomechanical Index (CBI) and Ambrósio Relational Thickness over the horizontal meridian (ARTh).[9]

The aim of the study is to assess the effect of intravitreal injection of ranibizumab (Lucentis) on corneal biomechanics by using Corneal Visualization Scheimpflug Technology (Corvis ST).

2. Patients and methods

This study is a prospective, interventional and nonrandomized study. It was carried out between June 2021 and August 2022 at Al-Zahraa University Hospital, National Eye Center, Rod Elfarag and the Research institute of Ophthalmology.

It included 30 eyes in 30 patients (21 (70 %) males, and 9 (30 %) females).

They were prepared and subjected to intravitreal ranibizumab injection as a treatment modality for their ophthalmic pathology which was reported as CNV in 13 eyes (8 males (26.66 %) and 5 females (16.66 %),Vein occlusion in 9 eyes (8 males (26.66 %) and 1 female (3.33 %) and DME in 8 eyes (5 males (16.66 %) and 3 females (10 %).

Table 5. Comparison between Corvis parameters before and after injection.

Corvis Parameters	Before injection	After injection	Difference	Test value[a]	*P*-value	Sig.
	No. = 30	No. = 30	Mean ± SD			
APPL1 length (mm)						
Mean ± SD	2.34 ± 0.33	2.26 ± 0.29	−0.09 ± 0.06	−1.480	0.150	NS
Range	1.86–2.86	1.88–2.77				
APP1 velocity (m/s)						
Mean ± SD	0.14 ± 0.02	0.15 ± 0.02	0.01 ± 0.00	1.639	0.112	NS
Range	0.1–0.17	0.11–0.18				
APP2 length (mm)						
Mean ± SD	2.15 ± 0.47	2.15 ± 0.35	0.00 ± 0.10	−0.035	0.973	NS
Range	1.48–3.1	1.89–2.97				
APP2 velocity (m/s)						
Mean ± SD	−0.25 ± 0.02	−0.25 ± 0.03	−0.01 ± 0.01	−0.886	0.383	NS
Range	−0.28 to −0.22	−0.32 to −0.2				
IOP (mm Hg)						
Mean ± SD	15.98 ± 2.20	17.9 ± 2.33	1.92 ± 0.13	2.227	0.030	S
Range	13.5–20.5	12.5–22.5				
bIOP (mm Hg)						
Mean ± SD	14.46 ± 1.72	16.02 ± 2.5	1.56 ± 0.78	2.095	0.04	S
Range	12.7–18.2	12.1–21.4				
Peak distance at HC (mm)						
Mean ± SD	4.94 ± 0.67	4.85 ± 0.31	−0.09 ± 0.13	−0.697	0.492	NS
Range	4.16–7.2	4.08–5.35				
Radius of highest concavity (mm)						
Mean ± SD	7.70 ± 0.66	7.84 ± 0.86	0.14 ± 0.10	1.407	0.170	NS
Range	6.31–9	6.21–9.2				

[a] Paired *t*-test.

For the patient's privacy, all participant names were obscured and replaced by code numbers.

Approval of Ethical committee at Al-Azhar University had been obtained. All the patients signed informed consent about the academic purpose of the study. They had the right of withdrawal from the study at any time if needed.

The study included Patients who are candidates for intravitreal ranibizumab injection (Lucentis) including those of recently recognized CNV, retinal vein occlusion and cystoid macular edema.

The exclusion criteria were as follows: positive history of corneal or intraocular surgery. History of eye trauma Corneal scars, Corneal dystrophy, Keratoconus, Retinal scar, Glaucoma, previous intravitreal injections, Vitro-retinal traction as evidenced by the OCT and Liver diseases.

All patients were subjected to data collection including age, sex, occupation, and past medical and surgical history. Testing the uncorrected visual acuity (UCVA) and best corrected visual acuity (BCVA) using Snellen's chart and auto refractometry. Slit lamp biomicroscope. Fundus examination using a 90 diopter lens after pupillary dilatation with tropicamide 1 % eye drops. Goldman applanation tonometry. Colored fundus photograph (if possible).

All patients were subjected to evaluation of corneal biomechanical parameters before intravitreal injection of ranibizumab using Corvis ST. (Corvis ST; Oculus Optikgeräte GmbH, Wetzlar, Germany- REF 72100).

Three CorVis readings of good quality were done for the study inclusion. The response profile quality was evaluated by an expert investigator using the manufacturer's standards.

The following parameters were measured by CorVis: IOP, bIOP, LAp1(first applanation length in mm), VAp1m/s (first applanation velocity), LAp2 mm, VAp2 m/s, pachymetry of the apex (pachy μm), amplitude of corneal deformation (HAD mm), peak distance between the two corneal peaks at highest concavity (PDHC mm), radius of curvature at highest concavity (RHC mm), Integrated radius, time of highest concavity of the cornea (THC ms), SSI, ARTh, CBI and DA ratio.

Three ranibizumab (0.5 mg/0.05 mL) injections were given intravitreally with 4-weeks intervals. (Ranibizumab, Lucentis made for F. Hoffmann, La Roche Ltd. Basel, Switzerland by Genentech Inc., San Francisco, CA-USA).

Re-evaluation of corneal biomechanical parameters was carried out one month after the 3-months course of the ranibizumab injection.

Table 6. Continue comparison between corvis parameters before and after injection.

Corvis parameters	Before injection	After injection	Difference	Test value	*P*-value	Sig.
	No. = 30	No. = 30	Mean ± SD			
DA (mm)						
Mean ± SD	1.05 ± 0.07	1.04 ± 0.13	−0.02 ± 0.02	−0.793[a]	0.434	NS
Range	0.94–1.19	0.64–1.26				
DA ratio						
Mean ± SD	4.33 ± 0.47	4.29 ± 0.42	−0.05 ± 0.08	−0.576[a]	0.569	NS
Range	3.5–5.6	3.5–5				
CCT (mm)						
Mean ± SD	558.93 ± 30.72	547.13 ± 43.42	−11.80 ± 5.59	−2.110[a]	0.044	S
Range	508–607	445–631				
Integrated radius						
Mean ± SD	7.49 ± 0.94	7.48 ± 0.78	−0.01 ± 0.09	−0.144[a]	0.886	NS
Range	6–9.6	6.1–9.5				
THC MD (ms)						
Mean ± SD	17.10 ± 0.88	17.13 ± 0.59	0.03 ± 0.79	0.185[a]	0.854	NS
Range	14.8–18	15.5–18				
SSI						
Mean ± SD	1.29 ± 0.18	1.29 ± 0.11	−0.01 ± 0.03	−0.203[a]	0.841	NS
Range	0.93–1.63	1.12–1.51				
ARTH						
Mean ± SD	526.80 ± 103.17	572.97 ± 108.83	46.17 ± 13.96	3.306[a]	0.003	HS
Range	353–779.3	324.1–776.7				
CBI						
Mean ± SD	0.22 ± 0.23	0.16 ± 0.17	−0.06 ± 0.02	−2.445[b]	0.014	S
Range	0.02–0.89	0.02–0.69				

[a] Paired *t*-test.
[b] Wilcoxon Rank test.

2.1. Statistical analysis

Data were acquired, reviewed, coded, and put into IBM SPSS version 23 of the Statistical Package for Social Science. The Paired *t*-test used to compare two paired groups with quantitative data and a parametric distribution, while Wilcoxon Rank test was used to compare two paired groups with nonparametric distributions. When the quantitative data were parametric, they were displayed as means, standard deviations (SD), and ranges; when they were nonparametric, they were displayed as medians and interquartile ranges (IQR).

P value was therefore deemed significant as follows: *P* greater than 0.05 is regarded as nonsignificant (NS), *P* less than 0.05 as significant (S), and *P* less than 0.01 as highly significant (HS).

3. Results

The present study is comprised of 30 eyes of 30 patients. Twenty (66.7 %) eyes were right, and 10 (33.3 %) were left. Twenty one (70 %) eyes for males and 9 (30 %) eyes were for females. Mean age was 59.60 ± 10.58 (Ranges: 25–72 years) Tables 1–4.

He table above demonstrates that the UCVA and BCVA improved statistically significantly after intravitreal injection of lucentis than before injection (*P* value < 0.001 and < 0.001, respectively) Table 5.

The above table shows that there was statistically significant increase in IOP and bIOP after injection than before injection (*P* value = 0.03 and 0.04, respectively) Table 6.

The above table shows that there was statistically significant decrease in CCT, CBI and increase in ARTh after injection than before injection (*P*-value = 0.044, 0.014, and 0.003, respectively).

3.1. Results of a case before IVI of Lucentis

Figs. 1 and 2.

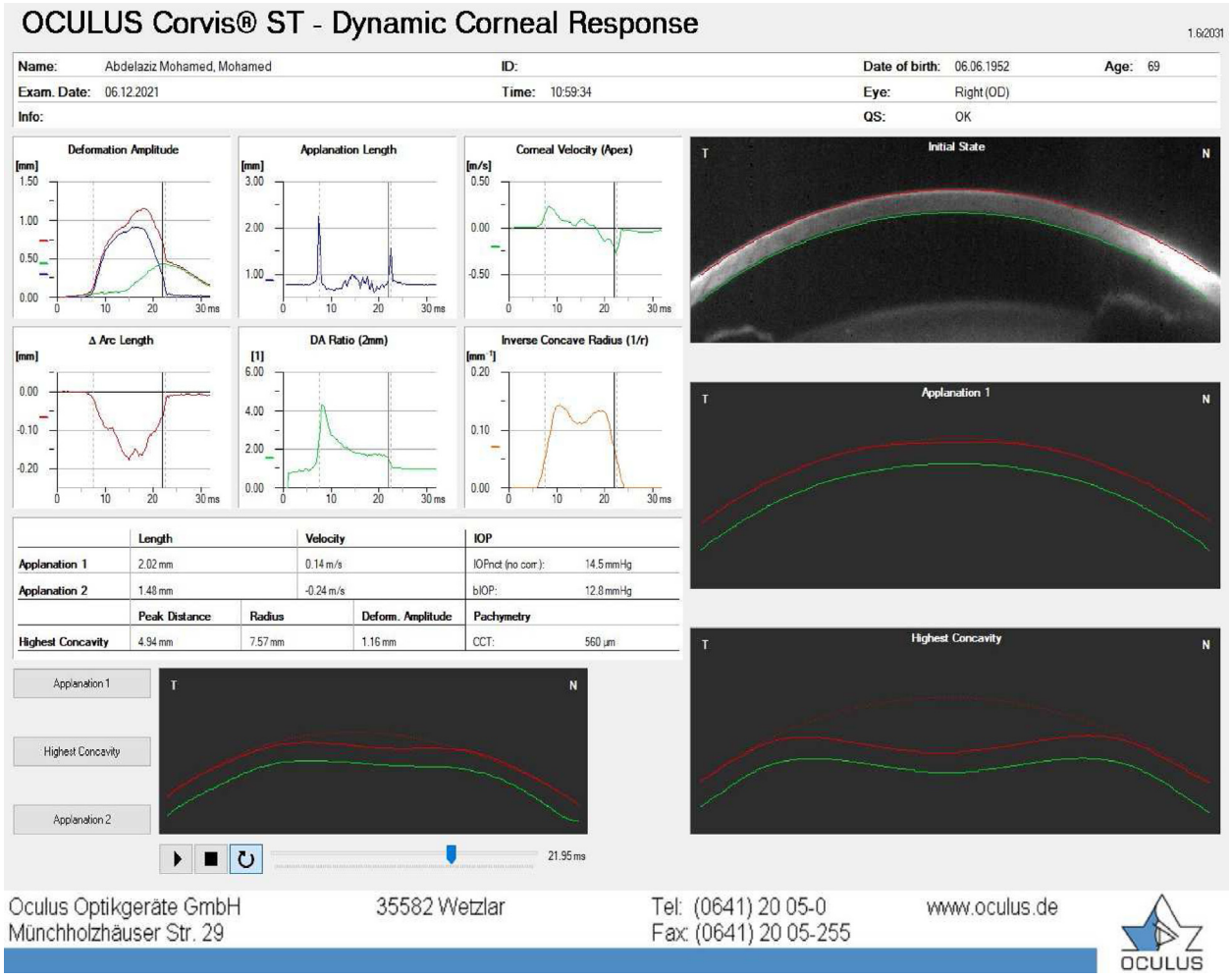

Fig. 1. Dynamic corneal response of a case before IVI of Lucentis.

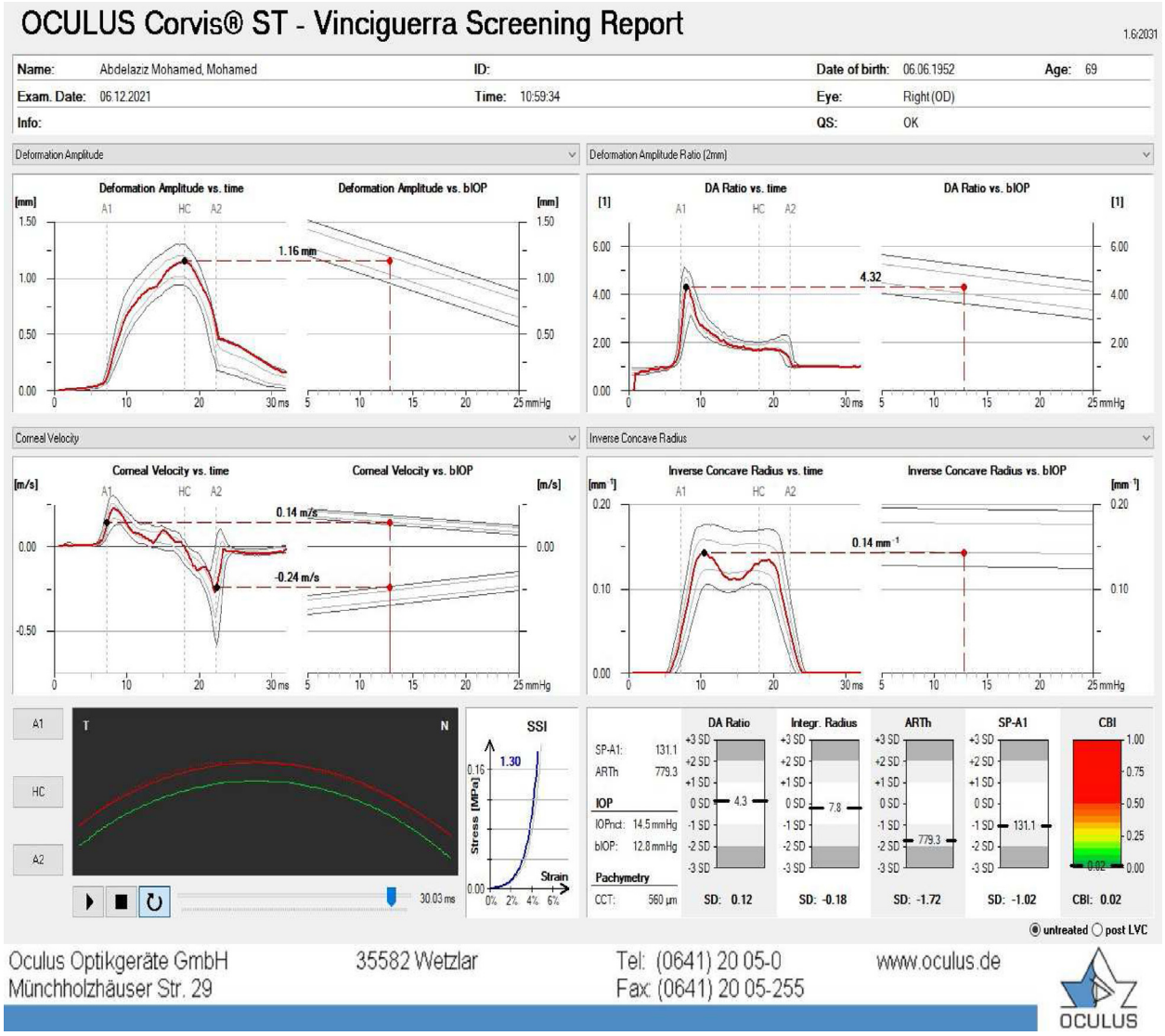

Fig. 2. Vinciguerra screening report of acase before IVI.

3.2. Results of the same patient after IVI

Figs. 3 and 4.

Results of the case shows increase in IOP and bIOP, decrease in CCT and decrease in CBI.

4. Discussion

The biomechanics of the cornea affect its functional responses and greatly affect vision. Assessment of corneal biomechanics is important in laser vision correction surgery screening, diagnosis of keratoconus and glaucoma.[10]

It is challenging to interpret the biomechanical characteristics of the cornea. Also, reaching accurate assessment of properties of cornea is not an easy mission due to the intricacy of the corneal viscoelastic biomechanical reaction.

In our study we measured corneal biomechanical parameters using the CorVis ST, a dynamic Scheimpflug analyzer device.

In this study, we reported statistically significant increase in IOP and bIOP 1 month after 3 months course of intravitreal injection than before injection (*P* values were 0.03 and 0.04, respectively), which is in accordance with the study reported by Shoeibi et al.[1]

In comparison to IOP by Corvis ST, Shoeibi et al.[1] also reported a statistically significant increase in IOP (ORAg, ORAcc) measured by ORA.

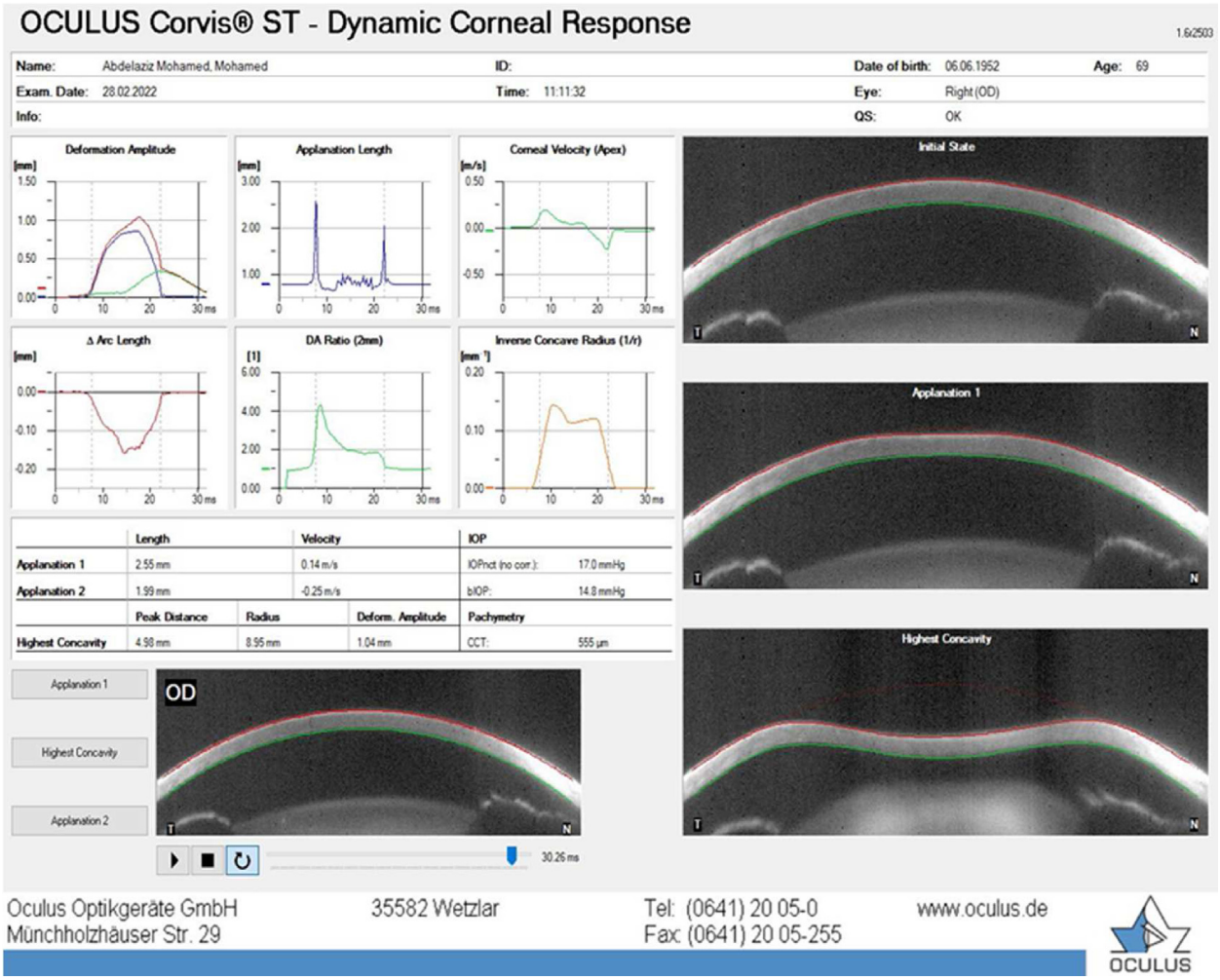

Fig. 3. Dynamic corneal response of the same patient after IVI.

Bekmez et al. [11], reported that there is a significant increase in IOP (ORAg, ORAcc) 24 h after injection as measured by ORA.

In our study we found that there is a significant increase in IOP that lasts up to 1 month after injection by corvis ST.

An interesting finding is the difference in CCT before and after injection. In our study there was a significant decrease in CCT after injection (*P* value was 0.044). This result is in accordance with the study reported by Shoeibi et al.[1]

As regards APPL1 Length there was statistically insignificant difference between before and after injection. (*P* value was 0.15) which is in accordance with the study reported by Shoeibi et al.[1]

In our study, APPL2 Length, APPL1 velocity, APPL2 velocity showed statistically insignificant differences before and after injection. These results disagree with the study reported by Shoeibi et al.[1] in which these parameters were at the border line of significance.

In our study, radius at HC, time of HC, peak distance at HC, deformation amplitude (DA) showed statistically insignificant differences before and after injection. These are in agreement with the study reported by Shoeibi et al.[1]

DA ratio, integrated radius, SSI showed statistically insignificant differences before and after injection in our study. When DA ratio, integrated radius parameters are high, they indicate that cornea is stiffer. In our study these parameters did not change significantly after injection.

ARTh, CBI showed statistically significant differences in comparison with the levels before injection. (*P* values were 0.003, 0.014, respectively).

DA ratio, integrated radius, SSI, ARTh, and CBI parameters need further studies in future.

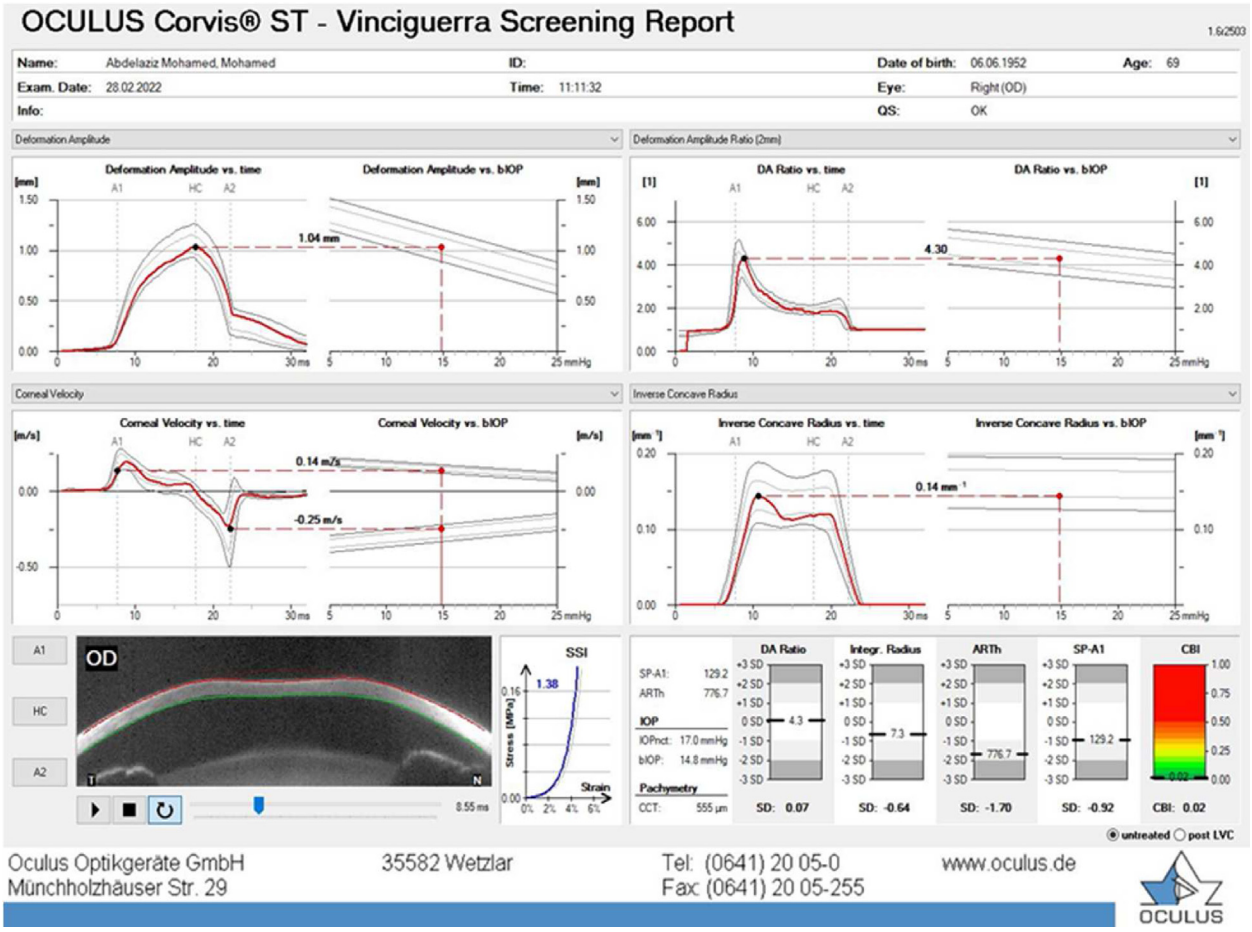

Fig. 4. Vinciguerra screening report of the same patient after IVI.

Lower values of ARTh (Ambrosio Rational thickness Horizontal) after injection than before injection, means that the cornea is stiffer. Also, lower values of CBI after injection than before injection, means an improvement in corneal biomechanics that was clear at 1 month after the 3 months course of ranibizumab injection.

4.1. Conclusion

In our study we evaluate the effect of intravitreal injection of anti-VEGF (ranibizumab) on corneal biomechanics. Results showed that there are statistically significant differences in some parameters, while other parameters showed non-significant statistically differences. The results showed that there is statistically significant rise in IOP and bIOP after injection, this change may not be permanent so further studies are needed. Also, there is significant decrease in central corneal thickness which correlates with the significant decrease in ARTH which means that the Cornea is stiffer, the lower is the ARTh, the stiffer is the cornea.

There was a significant decrease in CBI, which means improvement in corneal biomechanics.

Other parameters showed no statistically significant differences.

Disclosure

The authors have no financial interest to declare in relation to the content of this article.

Authorship

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Conflicts of interest

The authors declared that there were NO conflicts of interest.

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