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ORIGINAL ARTICLE

Effect of Corneal Collagen Cross Linking on Crystalline Lens Clarity Graded by Pentacam Nucleus Staging Software

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Abstract

Background: **Discuss the effect of ultraviolet rays (UVR) emitted during corneal collagen crosslinking (CXL) on cataract development in keratoconus patients in Cairo, Egypt.**

Methods: **We performed a study that describes the effect of CXL on human lens clarity, 100 eyes were investigated by oculus pentacam in the Egyptian Armed Forces Hospital at Kobri el Kobba in collaboration with Al-Azhar university hospitals diagnosed in January 2021.**

Results: **Our study reported that CXL has a highly significant effect in developing lens opacities especially the older age and small anterior chamber (AC) depth and reported also its affection on visual acuity (VA).**

Conclusion: **CXL results in significant changes and an increase in the densitometry of the crystalline lens which is a problem that increases the risk of the development of cataracts.**

Keywords: Cataract, Crosslinking, Crystalline lens, Pentacam

1. Introduction

Ectasia of the cornea is a worldwide disease affecting one in every 2000 of young patients.[1]

Keratoconus (KC) makes significant affection of the corneal curvature, lead to astigmatism which reduces the VA by image distortion, sensitivity to light, and glare.[2]

KC can be managed by different options, if it is stable, the idea is to correct the vision. If it is progressing, the main goal of management is to stop the progression.[3]

KC affects the corneal shape and leads to distortion and stromal thinning, so the traditional methods in management in the early stage are soft contact lenses (CL) and glasses.[2]

In another stage of ectasia, hard CL is the main method to improve the vision by impacting some fluid between it and the cornea, which makes the aberrations to be neutralized.[3]

The main intervention to stop the advancement of KC is collagen crosslinking (CXL).[4]

Dresden protocol for CXL, we get rid of the epithelium then apply riboflavin to bare cornea for half an hour then apply UVA for another 30 min1.

Another option for improving the vision is to implant a small curved PMMA rings in corneal stroma to flatten the curvature of the cornea, which is called corneal rings.[2]

The last option in the management of too thin cornea is completely replacing the whole layer or partial layers with a donor graft.[5]

Some studies reported that exposure of guinea pigs to UVA develops nuclear cataracts.[6]

Previously, ophthalmologists classified the grades of cataracts according to the old subjective method of classification called lens opacity classification three (LOCS III) but it relies on individual evaluation.[7]

So, we depended on Pentacam high resolution as a newly evolved objective method for the

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assessment of lens clarity which gives numerical values away from the other old subjective one.[7]

Pentacam nucleus staging (PNS) takes a series of images of the nucleus, forming a sample of the lens, and detecting its density according to the idea of light scattering, generating a grade of cataract from zero to five.[8]

The idea of measuring light scattering is a newly evolved technique to measure the optical density of the anterior segment of the eye.[9]

2. Patient and methods

2.1. Study design

A descriptive prospective study that detects the impact of the UVA emitted during the CXL of keratoconic corneas on the development of cataract and lens opacities, using PNS.

2.2. Setting and participants

The study was performed on 100 eyes of patients who attended Kobri el Kobba Hospital in collaboration with the Faculty of Medicine, Al Azhar University.

The study was performed from January 2021 to July 2022.

2.3. Procedure

Taking a full written informed consent before enrolment in the study and complete medical assessment of the participant.

Assessment includes history taking about the complaint, and past medical and ocular history.

Complete ophthalmological examination includes uncorrected, corrected visual acuity, pupillary function, color vision, slit lamp examination, and funduscopy.

Assessment of the KC using Oculus pentagram HR and PNS.

The inclusion criteria were age 15–40 years, both sexes, without any ocular or corneal diseases, KC confirmed by pentagram, post Lasik keratectasia, clear crystalline lens grade 0 was confirmed by PNS.

While the criteria that excluded the participants were age above 40 years and below 15 years, uncontrolled diabetes, autoimmune disorders, congenital lens opacities, early faint lens opacities approved by pentagram, occupational radiation (radiologist, dentist … etc.), previous operation other than refractive procedure, corneal diseases other than KC.

2.4. Ocular examination

Complete ocular examination includes corrected and uncorrected VA by log MAR chart, color vision, amsler grid, pupillary function, dilate the pupil by three drops of cyclopentolate, fundus examination, check the clarity of the crystalline lens to exclude any type of lens opacities.

2.5. Investigation performed

Pentacam HR type 70900 SN 98129080 was used in the study to evaluate the KC and detection of the clarity of the crystalline lens through its densitometry by schiempflug imaging, which was done preoperatively, first month and third month after CXL.

2.6. Technique of CXL

In this study we used the Epi off Dresden protocol, removing the epithelium to about 8 mm zone by soaking it with alcohol and then removing it by PRK blade, Imbibition of riboflavin 0.1 % isotonic (vibex) used in my study every 5 min, Application of UV rays of 8 mm spot diameter (OVEDRO KXL 11001018 KXL 1603082016) of UV-A light exposure of wavelength λ370 nm 3 mw/cm^2 for 30 min to be the total energy received 5.4 j/cm^2, the distance of the device from the eye is 5 cm, application of isotonic riboflavin every 5 min during UV application and Then contact lens applied and the patient prescribed vigamox ED, Nevenac ED and Polyfresh ED for 1week then prednisolone ED for two weeks then Fluca ED for 2 months. Patients were examined by slit lamp during follow-ups for epithelial healing and then CL removal 6th day post operatively.

During the first month and third month follow-ups, patients were captured by PNS densitometry.

2.7. Statistical analysis

In this study, we used specific measures to get the statistical analysis of the gathered values.

All of the data collected and managed for statistical analysis by (IBM SPSS) VERSION 23.

A paired *t*-test was used for comparison between the quantitative and parametric data.

ANOVA test used in comparison between more than two groups.

Assessment of the relation between two quantitative measures in the same group by spearman correlation.

The *P*-value was significant if *P* greater than 0.05: Nonsignificant *P* less than 0.05: Significant less than 0.01: Highly significant.

2.8. Ethical consideration

This study was approved by the research ethics committee at Al Azhar University at December 5, 2020, patients were informed about the study and signed a written consent.

3. Results

Participants of the study are of different ages and of both sexes as shown in (Table 1, Fig. 1).

Participants shared a common complaint which is a diminution of vision without past medical history, but others presented with a past ocular history of refractive surgery (LASIK) as shown in (Table 2, Fig. 2).

Hundredal 100 eyes participated in the study, 50 of them right and 50 of them left, with different visual acuity pre CXL (Table 3).

Precorneal thinnest location, AC depth, and lens densitometry range and mean documented by Pentacam and PNS pre CXL to detect the effect of CXL on them (Table 4).

PNS was done after CXL first month and third month to detect the changes in densitometry (Table 5).

This study shows a highly significant increase in lens densitometry first and third month postoperatively (Fig. 3).

The study revealed that there is a direct relation between age and preoperative densitometry (Table 6).

There is a highly significant change in the visual acuity after first m and third m in relation to the changes in densitometry as shown in (Table 7).

Table 1. Age and sex mean and range.

	No. = 50
Age	
Mean ± SD	27.48 ± 6.30
Range	15–40
Sex	
Female	23 (46.0 %)
Male	27 (54.0 %)

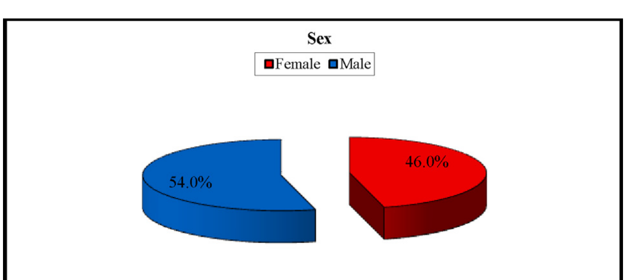

Fig. 1. Sex distribution.

Table 2. Table show history and examination data of the cases.

		No. (%)
Complain	Diminution of vision	100 (100.0 %)
Past medical history	–	100 (100.0 %)
Past ocular history	Lasik	20 (20.0 %)
Anterior segment of the eye	Lasik flap	20 (20.0 %)
Posterior segment of the eye	–	100 (100.0 %)

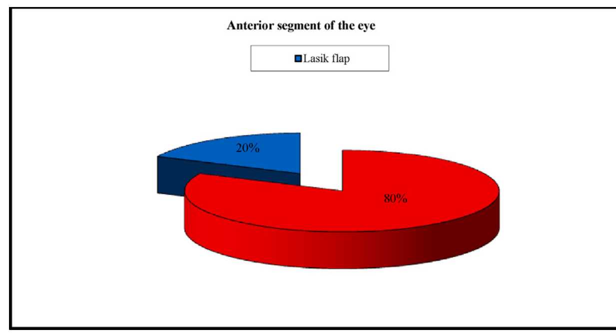

Fig. 2. Show 20 % of the participants had Lasik flap.

Table 3. Range and mean of visual acuity preoperatively.

	No. = 100
Eye	
OD	50 (50.0 %)
OS	50 (50.0 %)
Visual acuity	
Mean ± SD	0.54 ± 0.15
Range	0.3–0.9

The study revealed a highly significant increase in log MAR VA first month post CXL then rebound decrease in third month postoperative (Fig. 4).

The study results revealed that there is a significant direct relation between the densitometry and the affection of log MAR visual acuity as shown in (Table 8).

The following figures show the actual case of the study showing the PNS pre CXL grade zero (Fig. 5).

Table 4. Corneal thinnest location, AC depth and lens densitometry.

Pre	No. = 100
Corneal thinnest location	
Mean ± SD	457.38 ± 31.60
Range	399–565
AC depth	
Mean ± SD	3.20 ± 0.33
Range	2.5–4
Lens denistometry	
Mean ± SD	7.42 ± 0.94
Range	5.3–10.1

Table 5. Showing the effect of CXL first and third month on lens densitometry.

Lens denistometry	Pre No. = 100	1month No. = 100	3 month No. = 100	Test value[a]	*P*-value	Sig.
Mean ± SD	7.42 ± 0.94	8.37 ± 1.04	8.51 ± 1.03	360.409	<0.001	HS
Range	5.3–10.1	6.3–11.1	6.4–11.5			
Difference	–	0.94 ± 0.53	1.09 ± 0.46			
Paired *t*-test	–	17.890	23.748			
P-value	–	<0.001 (HS)	<0.001 (HS)			

[a] Repeated Measure ANOVA test.

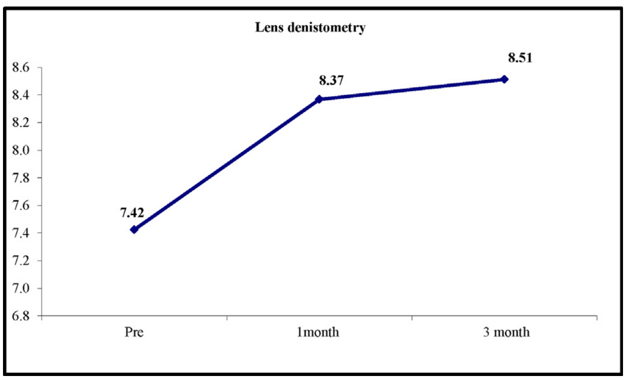

Fig. 3. Show the changes in lens densitometry first and third month.

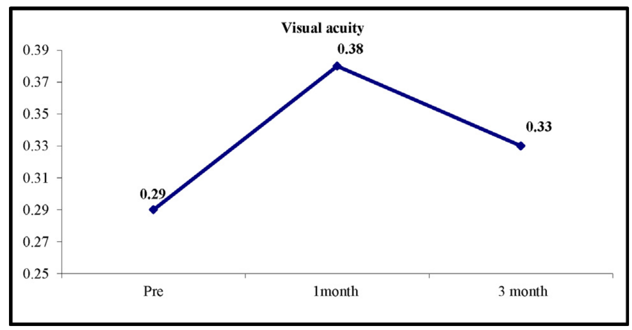

Fig. 4. Changes in log MAR visual acuity.

Table 6. Showing relation revealed in the study.

	Lens denistometry					
	Pre		Post 1 month		Post 3 month	
	r	*P*-value	r	*P*-value	r	*P*-value
Age	0.361*	0.010	0.411**	0.003	0.420**	0.002
Visual acuity	0.122	0.227	0.009	0.928	−0.049	0.630
Pre corneal thinnest location	0.031	0.759	−0.321**	0.001	−0.338**	0.001
Pre Anterior chamber depth	−0.202*	0.044	−0.088	0.383	−0.131	0.194

Pre CXL schiempflug image showing the numerical value of corneal and lens densitometry (Fig. 6).

Post CXL first month schiempflug image showing the changes in the numerical value of corneal and lens densitometry (Fig. 7).

Post CXL third month schiempflug image showing the changes in numerical value of corneal and lens densitometry (Fig. 8).

4. Discussion

This is the first study to evaluate the development of lens opacities after CXL graded by the newly evolved objective method.

There are three types of senile Cataracts cortical, nuclear, and subcapsular one.[10]

Risk factors for cataract development include acquired factors and congenital factors.[11]

Table 7. Visual acuity changes after first m and third m in relation to the changes in densitometry.

Visual acuity	Pre No. = 100	1month No. = 100	3 month No. = 100	Test value[a]	*P*-value	Sig.
Mean ± SD	0.29 ± 0.12	0.38 ± 0.18	0.33 ± 0.14	51.499	<0.001	HS
Range	0–0.5	0–1	0–0.7			
Difference	–	0.09 ± 0.10	0.04 ± 0.07			
Paired *t*-test	–	8.689	4.888			
P-value	–	<0.001 (HS)	<0.001 (HS)			

[a] Repeated Measure ANOVA test.

Table 8. Relation between lens denistometry and log MAR visual acuity.

Difference of visual acuity	Difference of lens denistometry			
	1month		3 month	
	r	*P*-value	r	*P*-value
1 month	0.569**	<0.001	–	–
3 months	–	–	0.537**	<0.001

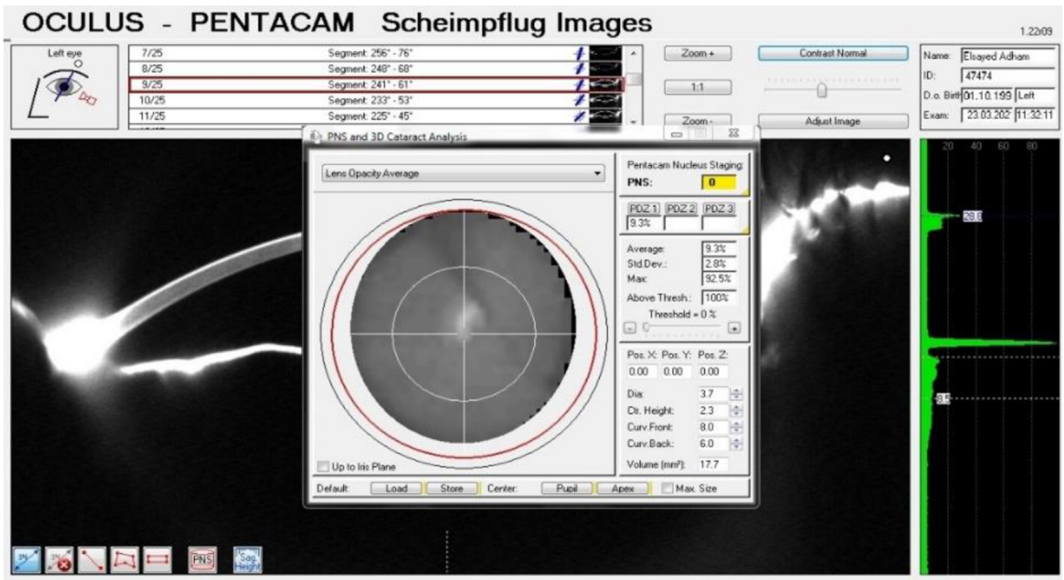

Fig. 5. Pre PNS show zero in red circle.

Aging, alcohol, smoking, increase in blood pressure, and irradiation are the main risk factors of cataract development.[10]

UVR causes lens opacification by denaturation of lens protein which leads to programmed cell death.[12]

Cornea absorbs 37 % of UVA rays, aqueous humor 14 %, and lens 48 %.[13]

In general, time exposure to UVA and UVB spectrum leads to a decrease in lens transparency.[11]

Cataracts cause visual impairment by light scattering in the opacities of the lens.[14]

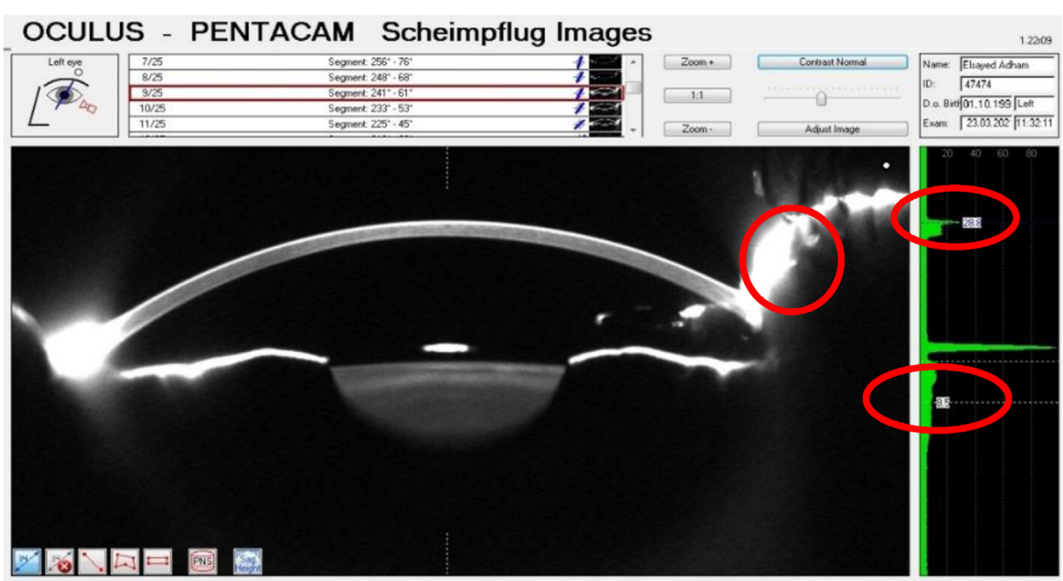

Fig. 6. Pre schiempflug image shows lens densitometry 8.5 and corneal 28.8.

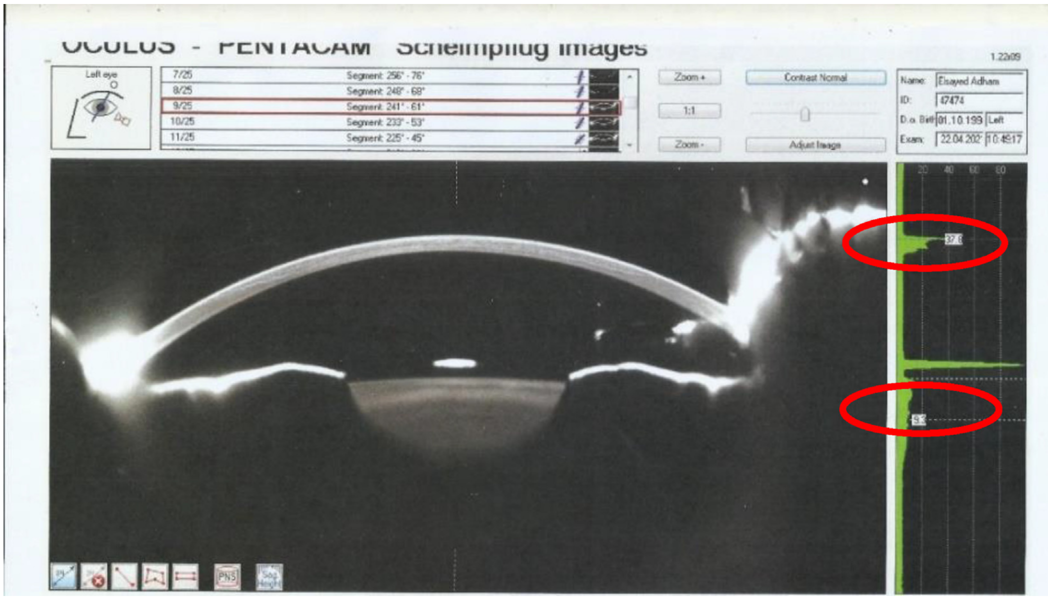

Fig. 7. Post first month lens densitometry 9.3 and corneal 37.8.

Many researchers reported that there's a great association between cataract development and UVR exposure which supports my study results.

Previously, Gakamsky reported that UVA induces nuclear cataracts in his animal experiment on a pig model.[15]

Gakamsky reported that there is a large effect on posterior subcapsular cataract development by UVA.[15]

People living in areas that have a large amount of UVA exposure lead to significant cataract development.[16]

Miyashita and colleagues found that there is less association between UVA and cataract development which is against my study results.[16]

Delavar and colleagues did several studies in France and North Africa and revealed there is a direct significant effect of UVR and cataract development which goes with my study results.[17]

Delcourt conducted studies in Australia and USA but Australian studies revealed that anterior cortical cataracts developed more than other types.[18]

Miyashita and colleagues reported no relation between outdoor UV exposure and cataract development which is against my study.[16]

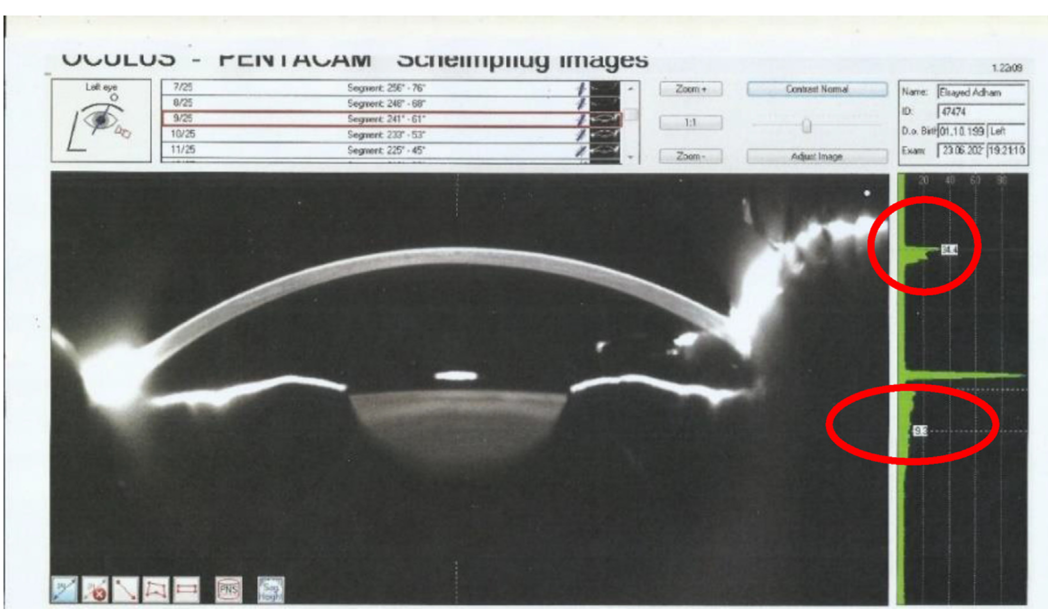

Fig. 8. Post third month lens densitometry 9.3 and corneal 34.4.

While McCarty and colleagues has found decreased or no risk which goes against my study and the other old studies.[19]

McCarty made a lot of studies in that field all over the world using rats, pigs and cows.[20]

Jaadane and colleagues found that the dose of irradiation of UVA that can induce cataract is 2.2 kJ/m^2.[21]

A lot of experiments were made on porcine eyes which is anatomically the same as human.[22]

Liu and colleagues did experiments on porcine lens ex-vivo which irradiated with wavelengths UVB and revealed that UVB has a very cataractogenic effect on crystalline lens.[11]

Dark field imaging revealed that UVA is more cataractogenic than UVB which goes with my study.[23]

In vivo irradiation of the crystalline lens of rodent animals revealed a significant effect of UVR on cataract development and bacterial growth in spite of the usage of Glycine-vancomycin-polymyxin-cycloheximide agar and intense irradiation, which support the cataractogenic effect of UVR.[24]

We must pay attention to the experiments conducted on the extracted animal lenses that the lens proteins begin to denature after only 5 h from the extraction.[25]

There are a lot of newly evolved methods of grading and early detection of cataract away from the old one that depends on the inspection of the lens color and the evaluation of the ophthalmologist such as slitlamp evaluation by LOCS classification.

Previously a lot of studies performed by scientists supporting my study to depend on new methods for grading and early detection of cataract away from the old one.

Because of the molecular basis of cataract formation, so it can be detected earlier by fluorescence methods.[11]

Depending on the amount of light scattering, newly objective method called dark field imaging was used for cataract assessment.[11]

So, there is a great interest of the scientist nowadays to measure the degree of the light scattering during its passage through the lens to get the degree of the cataract on objective numerical value.

So, I used a newly method for lens clarity assessment (PNS) away from the old method (LOCS3).

Reiss and colleagues used PNS for lens opacities assessment as an objective method of grading to detect the changes in the lens clarity depending on measuring the degree of light scattering.[26]

That is going with the aim of my study to use this method of grading of the lens clarity away from the old methods.

PNS is a good tool that can detect the degree of visual impairment induced by light scattering after passage of light through the lens opacities.[27]

My research revealed that there was a high association between UVR and lens opacities development, mostly due to denaturation of lens protein and apoptosis of lens cells fibers as Kamari reported in his study in 2019 which is powerful support of my study.

Mostly the energy dissipated from UVA during CXL lead to phototoxicity which lead to increase in the grade of nuclear cataract.

When the light pass through the lens opacities of the nuclear cataract leads to light scattering which leads to visual impairment, this may explain my study results in which there is decrease in VA in first and third month post CXL.

There are multiple drawbacks in my study, the small sample size, the all attention was paid to only one type of cataract which is the nuclear one without taking in consideration the other type of cataract and the short duration of follow-up.

Unfortunately, my study did not pay attention to sun protective equipment, iris color, and other types of cataract.

I recommend giving more attention to this worldwide ophthalmological problem and making more studies about the effect of UVR on development of cataract either during CXL or UVR exposure outdoors or medical staff exposed to UVR.

4.1. Conclusion

CXL results in high densitometry of human lens which lead to cataract development.

This is particularly in patient more exposed to UV rays and pre CXL high lens densitometry.

So, we recommend good screening for patient more subjected to UV rays and the AC depth and pre operatively lens densitometry.

Observational study

All authors contributed to the study's conception and design. Material preparation, data collection, and analysis. The first draft of the manuscript was written by all authors and also commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Contributions of authors

All contributors cooperated in collecting the data, and analyzing the results, the first draft of the manuscript was written by me, and then the editing was made by the other authors.

The last version of the manuscript was read and approved for publication by all authors.

Conflicts of interest

There are no any conflicts in this study.

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