Corneal biomechanical properties in patients with kidney transplant

Vaibhav Kumar Jain[1]*, Rachna Agarwal[1], Shabari Pal[1], Jaya Kaushik[2], Kumudini Sharma[1], Vikas Kanaujia[1]

Abstract:

PURPOSE: The purpose of the study was to evaluate the corneal biomechanical properties in patients post kidney transplant and to compare them with healthy age-matched control.

MATERIALS AND METHODS: In this cross-sectional study, 68 patients with kidney transplant (study group) and 68 healthy individuals (control group) were analyzed with ocular response analyzer measurements. Only the right eye of each participant was assessed for corneal hysteresis (CH), corneal resistance factor (CRF), corneal-compensated intraocular pressure (IOP_{cc}), and Goldmann-correlated intraocular pressure (IOP_g).

RESULTS: The mean CH in the study group was 9.70 ± 1.62 mmHg which was significantly lower than the control group with the mean CH of 10.60 ± 1.49 mmHg ($P = 0.001$). The mean IOP_{cc} was 18.17 ± 4.00 mmHg and 16.00 ± 3.94 mmHg in the study and control groups, respectively ($P = 0.002$). CRF and IOP_g were not significantly different between groups.

CONCLUSION: CH and IOP_{cc} are altered in kidney transplant patients.

Keywords:

Corneal biomechanical, corneal hysteresis, corneal resistance factor, intraocular pressure, kidney transplant, ocular response analyzer

[1]Department of Ophthalmology, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, Uttar Pradesh, [2]Department of Ophthalmology, Armed Forces Medical College, Pune, Maharashtra, India

*Address for correspondence:
Dr. Vaibhav Kumar Jain, Department of Ophthalmology, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow - 226 014, Uttar Pradesh, India.
E-mail: vaibhav.jainaiims@gmail.com

Introduction

Kidney transplantation is indicated in patients with chronic kidney disease (CKD) (Stage 5 or Stage 4) with progressive disease.[1,2] CKD may affect the ocular physiology, particularly in patients undergoing hemodialysis as suggested by previous studies.[3-5] Ocular alterations such as dry eyes, lower corneal endothelial cell count, increased central corneal thickness (CCT), reduced intraocular pressure (IOP), increased retinal nerve fiber layer thickness, and reduced choroidal thickness have been reported in such patients.[3-5] CKD is associated with low-grade persistent inflammation involving increased production of pro-inflammatory cytokines such as C-reactive proteins (CRPs), interleukin (IL)-1, IL-6, and tumor necrosis factor (TNF)-α.[6] Furthermore, an increased level of lysyl oxidase which is involved in collagen cross-linking has been reported in CKD patients.[7] After kidney transplant, these patients are put on prolonged immunosuppressive agents which may also affect the extracellular matrix components such as matrix metalloproteinases (MMP) and tissue inhibitors of MMP.[8,9] The corneal ultrastructural changes due to the altered pro-inflammatory cytokines, lysyl oxidase, and MMPs might affect the corneal biomechanics due to the altered extracellular matrix production and degradation. Commonly used immunosuppressive agents in renal transplant patients are corticosteroids, cyclosporin, tacrolimus, mycophenolate mofetil, azathioprine, and sirolimus.[10]

Long-term corticosteroid use is known to affect IOP.[11] Furthermore, biomechanical

characteristics of the cornea such as CCT[12] and corneal hysteresis (CH)[13] have been known to be related to IOP measurements and the risk of glaucoma progression. Since the IOP is the major and only modifiable risk factor for glaucoma diagnosis and treatment, it is of utmost importance to measure IOP least affected by other factors.

The ocular response analyzer (ORA) is a noncontact differential tonometer which measures IOP and corneal viscoelasticity *in vivo*.[14] We hypothesize that the corneal biomechanical properties may be altered in these subset of patients due to pathophysiological changes in stromal extracellular matrix constituents such as MMPs and pro-inflammatory cytokines which have been shown to be affected in CKD.[6,7,15] Therefore, this study aimed to analyze the distributions of the corneal biomechanical parameters in CKD patients who underwent kidney transplant as compared to age-matched controls, which has never been studied.

Materials and Methods

In this prospective cross-sectional study, the renal transplant patients >18 years of age who were undergoing routine follow-up visits at the nephrology department of our institute were recruited in the study. The study was performed as per the Declaration of Helsinki and ethics committee clearance was obtained from the institutional review board (IRB approval number:PGI/BE/534/2019).

Our study comprised 68 patients who underwent kidney transplant (study group) and 68 healthy age-matched individuals (control group). The control group comprised of a larger pool of volunteers. The patients were recruited over a duration of 1 year. Patients with existing corneal diseases, glaucoma, and retinal disorders were excluded from the study. Visual field examination (Humphrey Field Analyzer, Carl Zeiss Meditec, Inc., Dublin) and CCT tests were also performed as a part of glaucoma workup, to exclude the glaucoma disorders. Patients with other systemic diseases which may affect corneal biomechanical properties such as diabetes mellitus and immunological disorders were also excluded from the study.

Informed consent was obtained from all participants, and data were obtained with respect to age, sex, and duration of corticosteroid use in the study participants. These patients underwent complete ophthalmological assessment including ORA measurements. Only the right eye of all participants was assessed for the anterior and posterior segment using slit-lamp biomicroscope and slit-lamp biomicroscope with +90 D lens, respectively. All participants underwent CH, corneal resistance factor (CRF), corneal-compensated

intraocular pressure (IOP$_{cc}$), and Goldmann-correlated intraocular pressure (IOP$_{g}$) using ORA (Reichert Ophthalmic Instruments, Buffalo, NY, USA). To avoid discrepancies, ORA measurements were performed by a single experienced technician in the same room during a time period of 10:00 a.m.–12:00 p.m. The average of four values was taken for the study. The technician was blinded for the study and control groups to avoid bias.

The statistical analysis was performed using the Statistical Package for the Social Sciences (SPSSs) (SPSS Inc., Chicago, IL, USA) version 16. The mean (± standard deviation) and median (interquartile range) of various parameters were obtained. Independent sample *t*-test was used to compare the means of various variables. To detect the mean difference of 0.8 in CH between cases and controls, i.e. 9.7 ± 1.6 and 10.5 ± 1.5 (effect size = 0.52) (through estimation on 10-10 patients as a pilot study), at 80% power of the study and minimum two-sided 95% confidence interval, minimum required sample size for each of the two groups was came out to be sixty. Sixty-eight patients in each of the two groups were recruited. The sample size was estimated using software G Power version - 3.1.9.2 (Düsseldorf University, Germany).

Results

The mean age of the participants who underwent kidney transplant (study group) was 38.76 ± 9.19 years. The follow-up period of kidney transplantation ranged from 18 to 84 months (median of 30 months). The various demographic characteristics of the study group and control group are depicted in Table 1. No significant difference was observed in the mean best-corrected visual acuity (logarithm of minimum angle of resolution), mean age, and sex ratio ($P > 0.05$) [Table 1]. The etiological diagnosis for CKD is listed in Table 2. The most common diagnosis was diabetic nephropathy (thirty patients), followed by idiopathic, chronic glomerulonephritis, and tubulointerstitial nephritis. The immunosuppressive regimen of all patients comprised of oral prednisolone, cyclosporin, tacrolimus, and mycophenolate mofetil.

In corneal biomechanical properties measured by ORA, the mean CH in the study group was 9.70 ± 1.62 mmHg which was significantly lower than the control group with the mean CH of 10.60 ± 1.49 mmHg ($P = 0.001$). Similarly, the mean corneal-compensated IOP (18.17 ± 4.00 mmHg) in the study group was significantly different from the control group (16.00 ± 3.94 mmHg) ($P = 0.002$), whereas, the CRF (10.44 ± 1.83 mmHg in the study group and 10.85 ± 1.75 mmHg in the control group) and Goldmann-correlated IOP (17.07 ± 4.19 mmHg in the study group and 16.42 ± 4.22 mmHg in the control group) were not significantly different between the two groups.

Table 1: Demographic characteristics of study participants

Parameters	Study group (kidney transplant recipient)	Control group	P
Number of participants	68	68	
Mean age, years±SD	38.76±9.91	40.21±8.90	0.124*
Sex (male/female)	54/14	51/17	0.334#
Renal transplant duration (months) median, interquartile range	30 (18-84)	-	
Best-corrected visual acuity (log MAR)	0.20±0.26	0.14±0.14	0.115*

*Independent sample *t*-test, #Chi-square test. SD=Standard deviation, log MAR=Logarithm minimum angle of resolution

Table 2: Etiological diagnosis of chronic kidney disease patients with kidney transplant

Disease	Number of patients
Diabetic nephropathy	30
Chronic glomerulonephritis	14
Tubulointerstitial nephritis	7
Idiopathic	17

Table 3 shows the values of corneal biomechanical properties and their comparison between the two groups.

Discussion

The role of corneal biomechanical properties has been widely studied, especially in glaucoma and refractive surgeries.[16] It is altered in systemic diseases such as systemic lupus erythematosus, rheumatoid arthritis, scleroderma, and collagen vascular disorders.[17-20]

Kidney transplant patients have complex multifactorial systemic alterations due to the diseases process itself and also because of multiple immunosuppressive agents posttransplant. These advanced CKD patients are subjected to routine dialysis before kidney transplant and also on multiple immunosuppressive agents such as corticosteroid, cyclosporine, tacrolimus, mycophenolate mofetil, and azathioprine after kidney transplant. Patients with CKD have been shown to have persistently elevated acute-phase proteins such as CRP which indicates a chronic inflammatory stage.[6] Furthermore, there has been elevated level of inflammatory cytokines such as IL-1, IL-6, and TNF-α in these patients which have been shown to be associated with the deterioration of kidney function.[21] The overexpression of these inflammatory mediators in the corneal epithelium has been reported in corneal diseases such as pseudophakic corneal edema.[22] Similarly, lysyl oxidase has been found to be expressed in kidney tissue and is associated with tubulointerstitial fibrosis in CKD patients.[7] It plays an important role in extracellular matrix remodeling by promoting covalent cross-linking of collagen. It is possible that an increased level of inflammatory mediators and lysyl oxidase might alter the corneal tissue responsible for lower CH in our patients.

CKD patients have been shown to have altered MMPs which have been implicated in the pathogenesis of CKD.[15,23] These altered MMPs have also been implicated in corneal biomechanical changes in an earlier study of 45 patients of ocular graft versus host disease in patients with allogeneic hematopoietic stem cell transplantation.[24] This study showed significantly lower CH with a negative correlation with MMP-9 level.[24] Similarly, we also found significantly lower CH in our group of patients. Since the CH represents the viscoelastic properties of the corneal tissue, the possible changes in corneal stromal lamellae due to the overexpression of MMPs might be an explanation to this finding. The action of MMP-9 is proteolytic which is associated with the degradation of stromal extracellular matrix components. This dysregulation has been implicated in impaired corneal wound healing and keratolysis.[25,26]

Immunosuppressive agents after kidney transplantation might also be responsible for lower CH in our patients. Cyclosporin has also been shown to alter extracellular matrix production and degradation by decreasing Type I collagen synthesis and increase the MMP-9 activity causing further degradation in an experimental animal study.[8] The increased activity of MMP-2 and MMP-9 has been reported in lens epithelial cells and serum of patients with steroid-induced cataracts.[9] As cornea is rich in MMP-2 and MMP-9, it is possible that the altered collagen production and MMPs-induced collagenolytic action might be responsible for reduced CH in our patients.

Corneal biomechanical properties have become a very important factor to consider, particularly in these patients, as they are susceptible to the risk of steroid-induced glaucoma due to the prolonged steroid therapy in most of these patients. We found lower CH in our kidney transplant patients compared to controls, which has been shown as an independent risk factor for glaucoma diagnosis and management.[27] CH is related to corneal extracellular matrix components, so it is possible that the patients with lower CH might have lower stiffness of lamina cribrosa and peripapillary sclera due to lower scleral stiffness and collagen fiber organization which have been shown to be responsible for IOP-induced optic nerve head deformation in the computational model.[28] Furthermore, a higher IOP$_{cc}$ in kidney transplant patients shown in our study should be considered.

Table 3: Corneal biomechanical properties measured with ocular response analyzer

Parameters	Study group (kidney transplant recipient)	Control group	*P*
Corneal hysteresis (mmHg), mean±SD	9.70±1.62	10.60±1.49	0.001
Corneal resistance factor (mmHg), mean±SD	10.44±1.83	10.85±1.75	0.182
Corneal-compensated IOP (mmHg), mean±SD	18.17±4.00	16.00±3.94	0.002
Goldmann-correlated IOP (mmHg), mean±SD	17.07±4.19	16.42±4.22	0.367

SD=Standard deviation, IOP=Intraocular pressure

The relationship of CH and glaucoma has been shown by many previous studies.[16,29,30] This constitutes an independent factor for glaucoma progression and influences the IOP measurement too.[27] Low CH has also been reported in steroid-induced ocular hypertension in a previous study.[31] However, we reported lower CH in our kidney transplant patients who have not developed glaucoma or ocular hypertension but are at risk due to prolonged steroid therapy.[11] Steroids have been known to raise IOP and cause glaucoma by reducing aqueous outflow facility through multiple mechanism such as stabilization of lysosomal membrane and accumulation of polymerized glycosaminoglycans (GAGs) in trabecular meshwork causing biological edema, increasing the expression of extracellular matrix proteins such as GAGs, fibronectin, elastin, and laminin, thereby increasing trabecular meshwork resistance.[11,32,33]

Ours is the first study to assess the corneal biomechanical properties in CKD patients who have undergone kidney transplant. We enrolled 68 patients, which was more than the required sample size with power of 80%. However, our study had constraints. It is difficult to find whether these corneal biomechanical alterations in the study group are due to the steroid/other immunosuppressive agents or the disease itself. The comparison of corneal biomechanical properties before and after kidney transplantation could have explained the mechanism of these changes more clearly. Furthermore, we had relatively lesser number of participants too to draw any recommendation.

Conclusion

In our study, we found lower CH and higher corneal-compensated IOP in CKD patients with kidney transplant. This might be an interesting finding while routine evaluation of these patients for glaucoma. However, further large-scale studies are required for any guidelines.

Conflicts of interest
The authors declare that there are no conflicts of interests of this paper.

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