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ORIGINAL PAPER

Alterations in biomechanical properties of the cornea among patients with polycystic kidney disease

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Abstract

Purpose The aim of this study was to evaluate the corneal biomechanical features in polycystic kidney disease (PKD) patients and compare them with the healthy individuals.

Methods Totally 81 patients with a mean age of 48.46 ± 14.51 years and 60 control cases with a mean age of 44.68 ± 12.69 years were included in the study. All of the subjects underwent a complete ophthalmological examination, including visual acuity testing, biomicroscopic anterior and posterior segment examinations. Corneal hysteresis (CH), corneal resistance factor (CRF), Goldmann-correlated intraocular pressure (IOPg) and corneal-compensated intraocular pressure (IOPcc) were evaluated with the ocular response analyzer, and the central corneal thickness was evaluated with Sirius® corneal topography.

Results PKD patients had significantly increased CH values, without any alterations in IOP or CCT values, compared with the control cases (p:0.001). Among PKD patients, 23 were having liver cysts accompanying renal cysts. There was not any statistically significant difference between PKD patients with or without liver cysts regarding biomechanical properties of the cornea. However, both patient groups had statistically significantly increased CH values compared with the control cases.

Conclusion Patients with PKD present with higher CH values than age-matched controls. Larger studies are warranted to elucidate the alterations in corneal biomechanical properties and their clinical relevance in PKD patients.

Keywords Biomechanics · Cornea · Polycystic kidney disease

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Introduction

Polycystic kidney disease (PKD) is a group of monogenic disorders that result in renal cyst development. There are two major forms of PKD: autosomal

dominant PKD (ADPKD) and autosomal recessive PKD (ARPKD). Autosomal dominant type is mainly characterized by the progressive development of bilateral focal, renal cysts that may result in the end-stage renal disease (ESRD). It is a systemic disease, with the development of cysts also in the liver, pancreas, seminal vesicles, and arachnoid and with the accompanying intracranial aneurysms due to the involvement of vasculature [1].

Two main genes were defined in ADPKD, PKD1 (polycystin-1) (16p13.3) and PKD2 (polycystin-2) (4q21) [2]. On the other hand, ARPKD typically presents during the perinatal period with enlarged, echogenic kidneys. About one-third of the affected cases die at that period, and in others hypertension, renal insufficiency and biliary dysgenesis are the main signs [3]. Nevertheless, the diagnosis of ARPKD is not only restricted to neonatal period or childhood; it may also be diagnosed in adulthood, however, presenting with less severe kidney disease but with the complications of the liver disease. Along with the clinical picture, the gene responsible for the ARPKD development is also different from the ADPKD, PKHD1 (polycystic kidney and hepatic disease 1) (6q21) [4].

Many of the proteins involved in human PKDs comprising PKD1, PKD2 and fibrocystin have been localized to the primary cilia [5, 6]. Defects in ciliary function in PKD have been associated with the renal cyst formation and extrarenal involvements of PKD. The ciliary functions have been defined to be important also in retinal photoreceptor biology [7, 8]. Vision defects due to retinal degeneration were reported especially in syndromic forms of PKD [9]. Although, a direct etiology could not be defined; in the literature, some ocular abnormalities such as blepharochalasis and peripheral retinal pigmentation were reported in patients with polycystic kidney disease [10, 11].

The biomechanical features of the cornea, the elasticity, and rigidity, may be altered during the course of some diseases or due to some surgical interventions [12, 13]. Corneal involvement is defined in some systemic diseases such as systemic lupus erythematosus, rheumatoid arthritis or other inflammatory conditions, for example corneal ulcers associated with staphylococci infections, environmental bacteria able to invade different kinds of human cells [14–19]. Though the data about the ocular involvement of PKD are limited, polycystin-2 has also been detected in cornea and retina in an animal study but the clinical relevance of this finding warrants further studies [20].

Ocular response analyzer (ORA) and topography are the two main devices that provide significant information about the corneal biomechanical properties. Topography is essential in the determination of corneal surface pathologies such as keratoconus while ORA, a noncontact tonometer, provides the correct measurements of intraocular pressure and corneal biomechanical features that are very valuable in daily clinical practice [21].

The data concerning ophthalmological complications in the course of PKD are limited. To the best of our knowledge, especially alterations in corneal biomechanical properties in patients with PKD have not been studied in detail before. The aim of this study was to evaluate the corneal biomechanical features in PKD patients and compare them with the healthy individuals.

Materials and methods

Totally 81 PKD patients diagnosed with ultrasound in Nephrology department between January 2015 and December 2015 were involved in the study [22]. The control group consisted of 60 age- and gender-matched healthy individuals with normal upper abdominal ultrasound findings. Randomly selected eyes of each participant were evaluated. Excluding criteria were: contact lens wear, corneal scarring or pathology, refractive errors $\geq$2.00 diopters, ocular hypertension, glaucoma or suspect of glaucoma, ocular medications, retinal pathologies, pregnancy, lactation, undergoing hemodialysis and systemic medications affecting corneal thickness.

All of the subjects underwent a complete ophthalmological examination in the department of ophthalmology, including visual acuity testing, the intraocular pressure (IOP) assessment with the ocular response analyzer (ORA), topography and biomicroscopic examination. The ORA reports two IOPs: Goldmann-correlated IOP (IOPg) and corneal-compensated IOP (IOPcc) [23]. IOPg is equivalent to standard measurements of IOP by noncontact tonometry while IOPcc considers the biomechanical properties and does not dependent on the CCT. Corneal hysteresis (CH) and corneal resistance factor (CRF) were also evaluated with ORA. This device records two different

bidirectional (inward and outward) applanation pressure measurements using adjusted air pressure and a reflected infrared signal. The difference between these two pressures is the CH that is an indicator of corneal viscosity [24]. Corneal resistance factor is considered as the indicator of the overall resistance of the cornea that is mainly associated with the elastic properties of the cornea [25]. The waveform score (WS) was obtained by taking the average of four measurements with all the signals having a WS $\geq$6.0 [26].

Central corneal thickness measurements were performed using the Sirius® according to the manufacturer's instructions by the same trained examiner. The Sirius® (Costruzione Strumenti Oftalmici, Florence, Italy) is a topographic device which consists of a combination of two rotating Scheimpflug cameras and a Placido disk and allows full analysis of the topography and elevation of the anterior and posterior corneal surface and full corneal thickness [27].

Ethics

The procedures followed were in accordance with the ethical standards of the institutionally responsible committee on human experimentation and with the Helsinki Declaration of 1975, as revised in 2000. The study was approved by the local ethics committee (Ethics number: 2014-279). Informed consent was obtained from all individual participants included in the study.

Statistics

Statistical analyses of the results were performed using the SPSS software (version 21, IBM SPSS Statistics). Results were presented as mean ± SD for continuous variables and as proportions (%) for categorical variables. Student's t test or Chi-square test was used for the analyses. A p value of less than 0.05 was considered statistically significant.

Results

Totally 81 patients with a mean age of 48.46 ± 14.51 years and 60 control cases with a mean age of 44.68 ± 12.69 years were included in the study. The demographic features and corneal biomechanical features of study participants are summarized in Table 1.

Interestingly, patients with PKD had statistically significantly increased CH values compared with the control cases (CH = 9.66 ± 1.88 and 8.41 ± 2.40 respectively, $p = 0.001$) (Table 1).

Among patients, 23 were having liver cysts accompanying renal cysts. We also have evaluated the effects of the presence of liver cysts on corneal biomechanical features in the study group and compared the results with the control group (Table 2).

There was not any statistically significant difference between PKD patients with or without liver cysts (Table 2). However, CH was significantly higher than control cases both in patients without and with liver cysts ($p2 = 0.03$ and $p3 = 0.02$ respectively).

Discussion

This is the first study in the literature evaluating the corneal biomechanical factors in patients with PKD. In this study, we have evaluated the biomechanical features of cornea and determined that, although there were not any differences in intraocular pressure, corneal resistance factor and central corneal thickness in PKD patients, corneal hysteresis was statistically significantly higher compared with the control cases.

The intraocular pressure is the only "modifiable" risk factor in glaucoma. Taha et al. [28] reported two siblings with neonatal diabetes mellitus, congenital hypothyroidism, hepatic fibrosis, polycystic kidneys and congenital glaucoma and suggested the possibility of this combination of manifestations as a new autosomal recessive syndrome. However, any clear association between glaucoma or alterations in IOP measurements and PKD has not been reported before, as in our study. Liu et al. [29] investigated six genes, including polycystic kidney and hepatic disease gene 1 (PKHD1) that were suggested to be related to primary open-angle glaucoma (POAG) but did not determine any association between PKHD1 gene and POAG risk. In this study, we did not determine any alteration in IOP measurements between patients with PKD and healthy controls.

Corneal stroma is responsible for the mechanical and refractive properties of the cornea with its specific architecture [30]. The corneal hysteresis measurement

Table 1 Demographic features and corneal biomechanical features of study participants

	Polycystic kidney disease (*n*:81)	Control (*n*:60)	*p*
Gender (F/M)	44/37	39/21	0.23
Age (years)	48.46 ± 14.51	44.68 ± 12.69	0.11
IOPg (mmHg)	16.49 ± 3.94	15.97 ± 3.63	0.42
IOPcc (mmHg)	17.60 ± 4.61	16.25 ± 3.33	0.07
CH	**9.66 ± 1.88**	**8.41 ± 2.40**	**0.001**
CRF	10.06 ± 1.57	10.28 ± 1.48	0.40
CCT (microns)	538.11 ± 36.45	547.05 ± 31.13	0.13

F female, *M* male, *IOPg* Goldmann-correlated IOP, *IOPcc* corneal-compensated IOP, *CH* corneal hysteresis, *CRF* corneal resistance factor and *CCT* central corneal thickness

Table 2 Comparison of PKD patients with or without liver cysts with each other and control group in regard to corneal biomechanical features

	Polycystic without liver cysts (*n*:58)	Polycystic with liver cysts (*n*:23)	Control (*n*:60)	*p*1	*p*2	*p*3
Gender (F/M)	30/28	14/9	39/21	0.90	0.19	0.79
Age (years)	48.44 ± 15.58	48.47 ± 11.67	44.68 ± 12.69	0.72	0.15	0.15
IOPg (mmHg)	16.45 ± 4.03	16.59 ± 3.79	15.97 ± 3.64	0.88	0.50	0.55
IOPcc (mmHg)	17.61 ± 4.74	17.58 ± 4.38	16.25 ± 3.33	0.98	0.07	0.15
CH	**9.61 ± 1.83**	**9.78 ± 2.07**	**8.41 ± 2.40**	0.73	**0.03**	**0.02**
CRF	10.00 ± 1.45	10.21 ± 1.85	10.28 ± 1.48	0.59	0.31	0.87
CCT (microns)	538.35 ± 38.57	537.52 ± 31.25	547.05 ± 31.13	0.93	0.18	0.17

F female, *M* male, *IOPg* Goldmann-correlated IOP, *IOPcc* corneal-compensated IOP, *CH* corneal hysteresis, *CRF* corneal resistance factor and *CCT* central corneal thickness. Student's *t* test

*p*1 between polycystic without liver cysts and polycystic with liver cysts, *p*2 between polycystic without liver cysts and control and *p*3 between polycystic with liver cysts and control

indicates the ability of the tissue to absorb and disperse energy. Low corneal hysteresis is associated with optic nerve and visual field damage in glaucoma and the risk of structural and functional glaucoma progression. In addition, hysteresis may enhance intraocular pressure (IOP) interpretation: Low corneal hysteresis is associated with a larger magnitude of IOP reduction following various glaucoma therapies [31].

We have determined statistically significantly increased CH measurements in patients with PKD compared with the control cases which may be regarded as a decreased risk for glaucoma. Since corneal hysteresis was determined to be increased without any significant alterations in central corneal thickness, this increase may be associated with the structural changes in proteoglycans and glycosaminoglycans of the cornea that maintain the uniform corneal hydration and clarity [32]. Renal cyst formation has been associated with the defects in ciliary function in PKD [7, 8]. Many different genetic mutations have been identified in various ciliopathies including PKD1 and PKD2 [33]. Although retinal dystrophy has been associated with ciliopathies, the functions of cilia in viscoelastic properties of the cornea are not known exactly [34, 35]. Nevertheless, the alterations in ciliary functions may be associated with the increased CH values in PKD patients.

There was not any statistically significant difference between groups regarding CRF meaning that overall resistance due to both viscosity and elasticity was similar between two groups. In fact, CRF and CH generally are associated with the corneal resistance and alter in the same way. However, CH is the ocular resistance due to the combined effect of CCT, ocular

resistance and viscoelastic properties, while CRF is mainly determined by the elastic properties of the cornea and it is more closely associated with CCT [36]. We did not determine any significant alterations in CRF, though CH was significantly higher in PKD cases compared with the controls.

CCT is especially important in the evaluation of IOP readings [36]. The thinner the cornea, the lower the IOP readings artificially which may, in turn, result in undiagnosed glaucoma cases. We did not determine any significant alteration in CCT values between groups.

Liver cysts are the most common extrarenal manifestations accompanying PKD, but the presence of them is not associated with the prognosis [1]. Similarly, we did not determine any effects of liver cysts on biomechanical properties of the cornea.

There are some limitations of this study that should be mentioned. This is a cross-sectional study, and a direct cause and result connotation cannot be determined with this kind of studies. Secondly, the exact mechanisms causing these alterations should be studied in detail with also genetic and specular microscopic evaluations.

In conclusion, patients with PKD present with higher CH values than age-matched controls, without any alterations in IOP or CCT. Larger studies are warranted to elucidate the alterations in corneal biomechanical properties and their clinical relevance in PKD patients.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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