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Dry eye disease and tomographic parameters in keratoconus patients

Trockenes Auge und tomographische Parameter bei Keratokonus

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TABLE OF CONTENTS

LIST OF ABBREVIATIONS

µm	Micrometer
BUT	Break-up time in seconds
CAT	Conus apex thickness in µm
CCT	Central corneal thickness in µm
CKI	Center Keratoconus Index
D	Diopters
DED	Dry eye disease
IHA	Index of Height Asymmetry
IHD	Index of Height Decentration
IS	Inferior-superior dioptric asymmetry
ISV	Index of Surface Variance
IVA	Index of Vertical Asymmetry
K	Keratometry
KC	Keratoconus
KCI	Klyce/Maeda keratoconus index
KI	Keratoconus Index
KPI	Keratoconus prediction index
KSI	Klyce/Smolek keratoconus index
LASIK	Laser-assisted in situ keratomileusis
MKC	Mild Keratoconus
NIBUT	Non-invasive breakup time in seconds
PRK	Photorefractive keratectomy
S	Second
SAI	Surface asymmetry index
SKC	Severe Keratoconus
SRI	Surface regularity index
TEC	Time between eyelid closure in seconds
TIP	Time of first irregularities of Placido rings
TMS-5	Topographic Modeling System Number 5
TPT	Thinnest point thickness in µm
VA	Visual acuity

ZUSAMMENFASSUNG

Hintergrund und Ziel:

Keratokonus (KK) ist eine beidseitige, nicht entzündliche Erkrankung der Hornhaut des Auges und gehört zu der Gruppe der Hornhautektasien. Die Häufigkeit dieser Erkrankung in der Normalbevölkerung beträgt etwa 1:2000. Keratokonus zeichnet sich durch verschiedene klinische Symptome aus, jedoch können im Frühstadium diese noch fehlen und die korrekte Diagnose nur mittels Topographie gestellt werden. Es wurde kürzlich festgestellt, dass ein Mangel an Tränenflüssigkeit und chronisch trockene Augen einen Anstieg der Steilheit der inferioren Hornhaut und einen Astigmatismus hervorrufen können, der dem Keratokonus ähnelt.

Die Ziele unserer Studie waren:

- die Untersuchung des Zusammenhanges zwischen topographischen Parametern und trockenem Auge bei KK Patienten.
- der Vergleich der zentralen Hornhautdicke (CCT), der Spitze des Kegels (CAT) und der dünnsten Stelle (TPT) vermessen mit Scheimpflugaufnahmen und kontaktlosem Spiegelmikroskopie bei Keratokonuspatienten.

Methode: Es wurden 77 Augen von 49 Patienten mit Keratokonus (Alter 34 ± 12 Jahre) und 34 Augen von 34 gesunden Probanden (Alter 29,8 ± 7,5 Jahre) in der Klinik für Augenheilkunde, Universitätsklinikum des Saarlandes von Oktober 2010 bis März 2011 rekrutiert. Patienten mit vorangegangenen Augenoperationen oder Patienten, die Kontaktlinsen trugen, wurden ausgeschlossen. Die Untersuchungen der Patienten bestanden

aus der Bestimmung der Refraktion, der bestkorrigierten Sehschärfe, Spaltlampenbiomikroskopie, Hornhauttomographie, Keratometrie und Pachymetrie. Zur Beurteilung des trockenen Auges verwendeten wir den McMonnies Fragebogen, Schirmer Test, break-up time (BUT) und high-speed Videokeratoskopie.

Wir bestimmten mittels Pentacam (Pentacam HR, Oculus, Deutschland) den Surface Regularity Index (SRI), Surface Asymmetry Index (SAI) und Klyce/Maeda Keratokonus Index (KCI) und mittels des Topographic Modeling System (TMS-5, Tomey, Tennenlohe, Germany) den Index of Surface Variance (ISV), Index of Vertikal Asymmetry (IVA), Keratoconus Index (KI), Center Keratoconus Index (CKI), Index of Hight Asmmetry (IHA) und den Index of Height Decentration (IHD). Die Patienten wurden anhand der Pentacamdaten in zwei Gruppen eingeteilt, in eine Gruppe mit milder (Grad 1-2) und schwerer Form (Grad 3-4) des Keratokonus. Die High-Speed Videokeratoskopie wurde bei 26 Keratokonusaugen (10 Patienten mit leichtem und 16 Patienten mit schwerem KK) angewandt, um folgende Zielgrößen zu bestimmten: 1. den Ort und die Zeit bis zum Auftreten der Irregularität der Placido Ringe (TIP) und 2. die Zeit bis zum Lidschluss (TEC). Bei 77 Keratokonusaugen wurden CCT, CAT und TPT mittels Scheimpflug (Pentacam, TMS 5) und CCT mittels kontaktlosem Spiegelmikroskop (EM-3000, Tomey, Tennenlohe, Deutschland) gemessen.

Ergebnisse:

- Über 20% der Patienten mit Keratokonus (mittleres Alter 41 Jahre) fielen positiv im McMonnies–Test auf (mehr als 14,5 Punkte). Es zeigten sich keine signifikanten Unterschiede bei den Tränenfilmparametern zwischen den beiden Keratokonusgruppen ($P > 0,66$). Es bestanden keine Korrelationen zwischen SRI, SAI, KCI, ISV, IVA, KI, CKI, IHA, IHD und den Tränenfilmparametern (ausgeschlossen high-speed-Videokeratoskopie).

- Es bestand ein signifikanter Unterschied in beiden Gruppen mit Keratokonus zwischen CCT gemessen mit dem Scheimpflug-System und dem EM-3000 (P = 0,001) und zwischen CAT und TPT mit Pentacam und TMS-5 (P < 0,001). Für Patienten mit leichtem (R = 0,93, P = 0,0001) und schwerem (R = 0,72, P = 0,0001) Keratokonus zeigte sich eine signifikante Korrelation zwischen CCT gemessen mit der Pentacam und dem EM-3000. Für leichte bzw. schwere Keratokonus zeigte sich eine signifikante Korrelation zwischen CAT (R = 0,93, P = 0,0001 bzw. R = 0,85, P = 0,0001) und der TPT (R = 0,87, P = 0,0001 bzw. R = 0,94, P = 0,0001) mit dem Scheimpflug-System.

Schlussfolgerungen:

Nach dem 4. Lebensjahrzent zeigten mehr als 20% der KK Patienten Symptome eines trockenen Auges. Dies steht im Zusammenhang mit der Reduktion der Tränenproduktion, jedoch nicht mit einem Mangel an Lipidschicht. Es zeigte sich keine Korrelation zwischen den tomographischen Parametern und dem Syndrom des trockenen Auges. Tränenfilmparameter bei Keratokonuspatienten sollten in Zukunft noch detaillierter untersucht werden.

Unsere Studie zeigte, dass Messungen der CCT, CAT und TPT gemessen mit der Scheimpflug-Methode und kontaktlosem Spiegelmikroskop bei Keratokonuspatienten nicht austauschbar sind, aber in einander umgerechnet werden können. Dies kann eine Rolle spielen bei der Planung von Crosslinking oder dem Einsetzen von intrakornealen Ringen, da hier die genaue Angabe der Hornhautdicke Voraussetzung ist.

SUMMARY

Background and Purpose: Keratoconus (KC) is a bilateral, noninflammatory corneal ectasia with an incidence of approximately 1 per 2000 in the general population. Keratoconus shows clinical signs, but early stages of the disease may remain undiagnosed unless the corneal topography is studied. It was recently published, that chronic ocular desiccation and aqueous tear deficiency can produce inferior corneal steepening and high astigmatism mimicking keratoconus.

The aims of our study were twofold:

- to determine the interaction between corneal topographic parameters and dry eye disease in keratoconus (KC) patients
- to compare corneal thickness at the center (CCT), apex of the cone (CAT) and the thinnest point (TPT) assessed with Scheimpflug imaging vs. noncontact specular microscopy in keratoconus eyes.

Methods: Seventy-seven eyes of 49 patients with keratoconus (mean age: 34.3 ± 11.6 years) without history of ocular surgery or contact lens wear were enrolled in this study.

Routine ophthalmic examinations consisted of best corrected visual acuity measurement, slit-lamp examination, corneal tomography, keratometry and pachymetry. McMonnies questionnaire, Schirmer test, break-up time (BUT) and high-speed videokeratoscopy (during interblinking interval) were assessed to analyse dry eye disease.

In these 77 eyes we recorded surface regularity index (SRI), surface asymmetry index (SAI) and Klyce/Maeda keratoconus index (KCI) using the Topographic Modeling System (TMS-5, Tomey, Tennenlohe, Germany) and Index of Surface Variance (ISV), Index of Vertical Asymmetry (IVA), Keratoconus Index (KI), Center Keratoconus Index (CKI), Index of Height Asymmetry (IHA) and Index of Height Decentration (IHD) using Pentacam (Pentacam HR, Oculus, Germany). McMonnies questionnaire, Schirmer test and break-up

time (BUT) were used to analyse dry eye disease. Patients were subdivided into mild (grade 1-2) and severe stage (grade 3-4) KC groups according to Pentacam grading.

We also performed high-speed videokeratoscopy (during interblinking interval) in 26 eyes (10 eyes with mild keratoconus, 16 eyes with severe keratoconus). With high-speed videokeratoscopy the outcome measures were: (1) time of first irregularities of Placido rings (TIP), and (2) time of eyelid closure (TEC).

In 77 keratoconus eyes we recorded CCT, CAT and TPT readings using Scheimpflug imaging (Pentacam HR, Oculus, Germany and TMS-5, Tomey, Nagoya, Japan) and CCT with noncontact specular microscopy (EM-3000, Tomey, Nagoya, Japan).

Results:

- More than 20% of keratoconus patients were McMonnies positive (mean age 40.8 years). We did not find significant differences between patients with mild and severe KC in any of the examined tear film parameters ($P > 0.66$). There was no correlation between SRI, SAI, KCI, ISV, IVA, KI, CKI, IHA and IHD and any of the examined tear film parameters (without high-speed videokeratoscopy) neither in 77 KC patients nor in the 44 severe KC eyes.
- There was a significant difference in both groups of keratoconus between CCT measured using Scheimpflug systems and EM-3000 ($P = 0.001$) and between CAT and TPT using Pentacam and TMS-5 ($P = 0.008$). For mild ($R = 0.93$, $P = 0.0001$) and severe ($R = 0.72$, $P = 0.0001$) keratoconus patients there was a significant correlation between CCT measured with Pentacam and EM-3000. For mild or severe keratoconus groups was a significant correlation between CAT ($R = 0.93$, $P = 0.0001$ or $R = 0.85$, $P = 0.0001$) and TPT ($R = 0.87$, $P = 0.0001$ or $R = 0.94$, $P = 0.0001$) using Scheimpflug systems.

Conclusions:

- More than a fifth of keratoconus subjects may present dry eye disease after the

4th decade of life which is related to a reduction of tear production without lack of the lipid layer of the tear film. There is no interaction between dry eye disease and topographic changes in keratoconus. Tear film parameters of keratoconus patients should be analysed more in detail in the future.

- Our study showed, that CCT, CAT and TPT measurements using Scheimpflug imaging and noncontact specular microscopy should not be used interchangeably in mild and in a progressed stage of keratoconus, but could be transferred using a linear regression model. This might be important for planning crosslinking treatment or intracorneal rings, where sufficient corneal thickness is mandatory.

1. INTRODUCTION

1.1. Keratoconus

1.1.1. Definition of keratoconus

Keratoconus, which was first described in detail in 1854 [1] , derives from the Greek words Kerato (cornea) and Konos (cone). Keratoconus is the most common primary ectasia of the cornea.

It is a bilateral [2, 3] and asymmetric [4, 5] corneal degeneration characterized by localized corneal thinning, which leads to protrusion of the thinned cornea. Corneal thinning normally occurs at the inferotemporal and the central cornea [6].

Corneal protrusion causes high myopia and irregular astigmatism, affecting visual performance.

It usually becomes apparent during the second decade of life, normally during puberty [1, 3], although the disease has also been found to develop earlier [7] and later in life [1]. It typically progresses until the fourth decade of life, when it usually stabilizes [1]. A recent study has determined that 50% of nonaffected eyes of subjects with unilateral keratoconus will develop the disease in about 16 years [8].

1.1.2. Epidemiology

The incidence and prevalence in the general population has been estimated to be between 5 and 23%, and 5.4 subjects per 10.000, respectively [1, 3, 9]. The reported differences in incidence and prevalence are attributed to different definitions and diagnostic criteria employed between studies.

However, it would not be surprising to expect an increase in the incidence and prevalence rates of this disease over the next few years with the current wide spread use of corneal topography leading to improved diagnostics. Keratoconus affects both genders, although it is

unclear whether significant differences between males and females exist [10]. Keratoconus is also known to affect all ethnicities [1, 11-13].

In a study conducted in the Midlands area of the United Kingdom, a prevalence of 4:1, and an incidence of 4.4:1 was found in Asians compared to Caucasians [14]. In another study, undertaken in Yorkshire, the incidence was 7.5 times higher in Asians compared to Caucasians. The latter was hypothesized to be attributed to consanguineous relations, especially first-cousin marriages, which commonly take place in the Asian population of the area assessed [15].

1.1.3. Etiology

Etiology is unknown and most likely multifactorial. Several studies have reported a strong association between eye rubbing and the development of keratoconus [1, 12, 16-18]. This association may be due to the activation of wound healing processes and signalling pathways secondary to mechanical epithelial trauma and also mechanical trauma of keratocytes or even increased hydrostatic pressure in the eye [19]. Contact lens wear is another form of corneal microtrauma associated with keratoconus [20]. The hereditary pattern is not predictable although the strongest evidence of genetic involvement is a high concordance rate in monozygotic twins [21]. A positive family history has been reported in 6-8% of the cases and its prevalence in first-degree relatives is 15-67-times higher than the general population [22]. In addition, unaffected first-degree relatives have a higher rate of abnormal topography compared with the general population [23]. The genetic basis of keratoconus has been studied through linkage mapping and mutation analysis to reveal its molecular basis and pathogenesis. Mapping studies have identified a number of loci for autosomal-dominant inherited keratoconus: 20p11-q11 [24, 25], 16q22.3-q23.1 [26], 3p14-q13 [27], 2p24 [28], 15q22.32-24[29, 30], and 5q14.3-q21.1[31], other potential loci have also been reported [32, 33], indicating genetic heterogeneity.

1.1.4. Classification

Several classifications of keratoconus have been proposed in the literature, based on morphology, disease evolution, ocular signs and index based systems.

Morphological classification

Classically, KK has been classified as follows. [1, 34, 35]:

- *Nipple* - The cone has a diameter ≤ 5 mm with round morphology and is located in the central or paracentral cornea, more commonly at the inferonasal corneal quadrant. Correction with contact lenses is normally relatively easy.

- *Oval* - The cone has a diameter > 5 mm and a paracentral to peripheral location, more commonly at the infero-temporal corneal quadrant. Contact lens correction is more difficult.

- *Keratoglobus* - The cone is located throughout 75% of the cornea. Contact lens correction is a difficult challenge, except in very limited cases.

Disease evolution based classification

The first keratoconus classification based on disease evolution was proposed by Amsler [10], who classified the disease in four different stages (**Table 1**).

Stage	Description
1	Fruste or subclinical form; diagnosed by corneal topography; 6/6 VA achievable with spectacle correction.
2	Early form; mild corneal thinning; corneal scarring absent.
3	Moderate form; corneal scarring and opacities absent; Vogt's striae; Fleischer's ring; < 6/6 VA with spectacle correction, but ~ 6/6 VA with contact lens correction; irregular astigmatism between 2.00 - 8.00 D; significant corneal thinning.
4	Severe form; corneal steepening > 55.00 D; corneal scarring, < 6/7.5 VA with contact lens correction; severe corneal thinning and Munson's sign.

Table 1. Keratoconus classification based on disease evolution. VA - visual acuity, D - Diopters.

Index – based classification systems

Disease detection, even at early stages, has become increasingly important particularly in an attempt to prevent iatrogenic ectasia formation in patients with subclinical forms of keratoconus who underwent refractive surgery procedures [36-38]. For this reason, several index-based classification methods have been developed based on corneal topography systems [23, 39-45] (**Table 2**).

Author	Index	Point of cut	Description
Rabinowitz/McDonnel [23]	K Value I-S Value	47.2 1.4	Diagnosis is performed based on the central keratometry and the inferior-superior assymmetry in keratometric power
Maeda/Klyce [40]	KPI KCI%	0.23 0%	KPI is derived from eight quantative videokeratography indexes. KCI% is derived from KPI and other four indexes.
Smolek/Klyce [41, 42]	KSI	0.25	Keratoconus detection and the level of severity is assessed using an artificial intelligent system.
Schwiegerling/ Greivenkamp [43]	Z3	0.00233	Diagnosis is performed based on videokeratoscopic height data decomposed into orthogonal Zernike polynomials.
Rabinowitz/Rasheed [44]	KISA%	100%	Diagnosis is derived from K value, I-S value, AST and SRAX.
McMahon et al. [35]	KSS	0.5	Diagnosis is performed based on slit-lamp findings, corneal topography, corneal power and higher order first corneal surface wavefront root mean square error.
Mahmoud et al. [45]	CLMI	> 0.45	Diagnosis based on detecting the presence or absence of keratoconic patterns and determining the location and magnitude of the curvature of the cone.

Table 2. Index-based systems for keratoconus detection. A higher value than the treshold suggests the presence of keratoconus.

1.1.5. Clinical features

The ocular symptoms and signs of keratoconus vary depending on the severity of the disease. At incipient stages, also referred to as subclinical or frustre forms, keratoconus normally does not produce any symptoms and thus could remain undiagnosed by the patient and practitioner unless specific tests are undertaken for diagnosis [46]. Disease progression is manifested by a significant loss of visual acuity, which cannot be compensated with spectacles. Therefore, eye care practitioners should be suspicious about the presence of keratoconus when a visual acuity of 6/6 or better is difficult to achieve with increasing against-the-rule astigmatism [1]. Near visual acuity is generally found to be better than expected from the refraction, distance visual acuity and age of the patient. The appearance of "scissors" shadows while performing retinoscopy also suggests the development of irregular astigmatism. Though retinoscopy it is possible to estimate the location of the cone's apex and its diameter, and the adjustable spectacle corrected visual acuity is achievable. Keratometry readings are commonly within the normal range, but may appear irregular. The thinnest part of the cornea is normally located off the visual axis, is also a common sign preceding ectasia.

In moderate and advanced cases of keratoconus, a hemosiderin arc or circle line, commonly known as *Fleischer's ring*, is frequently seen around the cone base [10]. This line has been suggested to be an accumulation of iron deposits from the tear film onto the cornea as a result of severe corneal curvature changes induced by the disease and/or due to modification of the normal epithelial slide process [47]. Another characteristic sign is the presence of *Vogt's striae*, which are fine vertical lines produced by compression of Descemet's membrane, which tend to disappear when physical pressure is exerted on the cornea digitally [48] or by gas permeable contacts lens wear [49].

The increased visibility of corneal nerves and observation of *superficial and deep corneal opacities* are also common signs, which might be present at different stages of the disease [48].

The majority of contact lens patients eventually develop corneal scarring. Munson's sign, a V-shape deformation of the lower eyelid when the eye is in downward position, and a Rezzuti's sign, a bright reflection of the nasal area of the limbus when light is directed to the temporal limbus area, are signs frequently observed in advanced stages [48]. Breaks in Descemet's membrane have also been reported in severe keratoconus, causing acute stromal oedema or «hydrops» [39].

1.1.6. Histopathology

Histopathologically, there are three signs which typically characterize keratoconus: 1) stromal corneal thinning; 2) Bowman's layer breakage; and (3) iron deposits within the corneal epithelium's basal layer [1, 9].

In keratoconus disease, the corneal epithelium's basal cells degenerate and grow towards Bowman's layer. This can be noted by observing accumulation of ferritin particles into and between epithelial cells [50]. Basal cell density is also decreased in comparison to normal corneas [51]. Bowman's layer often shows breakages, which are filled with collagen from the stroma and positive nodules of Schiff's periodic acid. They form Z-shaped interruptions due to collagen bundle separation [52]. In the stroma, a decrease in the number of lamellae and keratocytes, degradation of fibroblasts [52], changes in the organisation of the lamellae, and uneven distribution of collagen fibrillar mass, particularly around the apex of the cone have been observed [53]. Studies carried out using confocal microscopy have demonstrated a reduction in the number of keratocytes in keratoconus compared to normal subjects; the reduction seems to be more pronounced in more advanced disease [54]. Descemet's membrane is usually unaffected, except in cases of breakages of this tissue. The endothelium is also generally unaffected by the disease [51], although pleomorphism and endothelial cells pointing towards the cone have been reported [52]. It has also been demonstrated that corneal nerves in

keratoconus have thicker fibre bundles, reduced density, and subepithelial plexus compared to normal subjects [55].

1.1.7. Management and treatment

Keratoconus management varies depending on the disease severity. Traditionally, incipient cases are managed with spectacles, mild to moderate cases with contact lenses, and severe cases can be treated with keratoplasty. Other surgical treatment options include intra-corneal rings segments, corneal cross-linking, laser procedures (i.e., photorefractive keratectomy, phototherapeutic keratectomy), intra-ocular lens implants or combinations [10].

1.2. Dry eye disease

1.2.1. Definition of dry eye disease

Dry eye disease is one of the most frequently encountered ocular morbidities, a growing public health problem and one of the most common conditions seen by eye care practitioners [56]. In the light of new knowledge about the roles of ocular surface inflammation and tear hyperosmolarity in dry eye and the effects of dry eye on visual function, the International Dry Eye Workshop (DEWS) defined dry eye as a "multifactorial disease of the tears and ocular surface that results in symptoms of discomfort, visual disturbance, and tear film instability with potential damage to the ocular surface. It is accompanied by increased osmolarity of the tear film and inflammation of the ocular surface" [57].

1.2.2. Epidemiology

Each of the population-based studies used a different definition of dry eye. Some studies included objective examination, but many did not. Nevertheless, in view of the poor performance (inconsistency, lack of repeatability, etc) of commonly used clinical tests and the importance of symptoms as an indicator of both the clinical and public impact of dry eye, these data from large epidemiological studies have provided highly relevant/required information on the prevalence of dry eye. The studies were performed in different populations across the world and therefore, provide some valuable information regarding potential differences in dry eye according to geographic regions. In particular, data from the two studies performed in Asia suggest the possibility of a higher prevalence of dry eye in those populations. The weight of the evidence from large epidemiological studies indicates that female sex and older age increase the risk for dry eye; the Salisbury Eye Evaluation study is the most notable exception. An overall summary of data suggests that the prevalence of dry eye lies somewhere in the range of 5-30% in the population aged 50 years and older [58].

1.2.3. Etiology

The last decade has brought significant improvement in the understanding of the etiology and pathogenesis of dry eye [59]. Appreciation of the role of inflammation in this syndrome was one of the most important factors that aided in the understanding and treatment of dry eye disease (DED). The findings of the association of inflammation with reduced tear secretion and subsequent damage to the ocular surface led to the proposal of a unified concept of DED [60]. Older age and female sex (particularly peri- and postmenopausal age) are well known risk factors for DED [58, 61]. Hormonal studies suggest that sex hormones influence ocular surface conditions through their effects on tear secretion, meibomian gland function, and conjunctival goblet cell density [62]. Chronic androgen deficiency is associated with meibomian gland dysfunction. Postmenopausal women who use hormonal replacement therapy (HRT) - especially oestrogen alone, have a higher prevalence of DED compared with those who have never used HRT [63, 64]. Other factors that precipitate and/or exacerbate DED include long-term contact lens wear, refractive surgeries such as laser-assisted in-situ-keratomileusis (LASIK) or photorefractive keratectomy (PRK) [58, 65, 66], smoking [67], extended visual tasking during computer use, television watching and prolonged reading [68, 69].

Dry eye can be worsened by low relative humidity (RH) conditions like office environment, air-conditioning, airplane cabins and extreme hot or cold weather [70, 71]. Certain systemic medications can cause dry eye [58]. Frequent use (> 4-6 times daily) of preserved eye drops (including glaucoma medications and artificial tears) may contribute to DED because of the well established toxicity of preservatives like benzalkonium chloride [72].

1.2.4. Diagnosis and classification

Traditionally, combinations of diagnostic tests are used to assess symptoms and clinical signs [73].

1.2.4.1. Tear film stability assessment

Tear film stability assesment is commonly done by performing break-up-time (BUT). Values of <10 seconds have traditionally been considered abnormal. Non-invasive breakup time (NIBUT) is a test of tear stability that does not involve the instillation of fluorescein dye. Measurements are performed with a xeroscope or keratometer [74].

1.2.4.2. Ocular surface integrity

Fluorescein, Rose Bengal and lissamine green are the dyes used to view any conjunctival and corneal abnormalities [74, 75]. The staining pattern can be photographed and graded using one of several scoring systems [73]. Van Bijsterveld scoring system is used for Rose Bengal dye. Intensity of staining is scored at two exposed conjunctival zones (nasal and temporal) and at the cornea. Score of 3 is given for each zone where 0 is for no stain, +1 for separate spots, +2 for many separate spots, and +3 for confluent spots, with a maximum score of 9.

1.2.4.3. Aqueous tear flow

It is commonly assessed by performing a Schirmer test which is of two types. Schirmer 1 (without topical anaesthesia) to measure reflex tearing and Schirmer II, also known as Jone's test (with anaesthesia) to measure basal tearing by minimizing ocular surface reflex activity. Value of less than 6 mm of strip wetting in 5 minutes is accepted as diagnostic marker for aqueous tear deficiency [74].

1.2.4.4. Other diagnostic tests

- Fluorescein clearance: This test measures tear clearance or turnover. Delayed clearance has been associated with increased tear cytokine concentration, which may contribute to chronic inflammation [76].

- Corneal topography: A number of non-invasive techniques like videokeratography may be useful as an objective test for diagnosing and evaluating the severity of DED [77, 78].

- Impression cytology: This test serves as a minimally invasive alternative to ocular surface biopsy. Superficial layers of the ocular surface epithelium are collected (e.g. by applying filter paper) and examined microscopically. Impression cytology is useful for detecting abnormalities such as goblet cell loss and squamous metaplasia [79].

Although useful for confirming the diagnosis, the above diagnostic test results correlate poorly with symptoms [58].

- Tear hyperosmolarity is a global mechanism of DED. It is clear from the comparison of the diagnostic efficiency of various tests for DED, used singly or in combination, that osmolarity could potentially provide a "gold standard" for DED diagnosis [80].

Physical examination includes visual acuity measurement, external examination, and slit-lamp biomicroscopy for grading the severity of DED [81, 82].

1.2.5. Clinical features

Common DED symptoms are dry, scratchy, gritty or sandy feeling, foreign body sensation, pain or soreness, burning, itching and increased blinking [83]. Two complaints provide important clues that patients may be suffering from dry eye: exacerbation of irritation by

environmental stress and exacerbation of irritation by activities that require prolonged visual attention.

A number of questionnaires are available for evaluation of various aspects of DED symptomatology, including severity, effect on daily activities and quality of life. The ocular surface disease index (OSDI) [84] permits quantification of common symptoms and provides a reasonably objective approach to the evaluation of symptoms over time. It is a valuable tool in clinical treatment trials [57].

In our study we used McMonnies questionnaire (**Appendix 1**).

The **McMonnies questionnaire**

Please answer the following by underlining the appropriate response;

1. **Female** **Male**
2. **Under 25 years** **25 to 45 years** **Over 45 years**
3. **No CL wear** **Wear soft CL** **Wear hard CL**
4. **Have you ever had drops prescribed, or other treatment, for dry eyes?**
   Yes No Uncertain
5. **Do you ever experience any of the following eye symptoms?**
   Soreness Scratchiness Dryness
   Grittiness Burning
6. **How often do your eyes have these symptoms?**
   Never Sometimes Often Constantly
7. **Are you eyes *unusually* sensitive to cigarette smoke, smog, air conditioning, or central heating?**
   Yes No Sometimes
8. **Do your eyes easily become very red and irritated when swimming**
   Yes No Sometimes Not applicable
9. **Are your eyes dry and irritated the day after drinking alcohol?**
   Yes No Sometimes Not applicable
10. **Do you take any of the following?**
    Antihistamine Diuretics Sleeping tablets Tranquilizers
    Oral contracept. HBP meds Ulcer meds

11. Do you suffer from arthritis?

Yes No Uncertain

12. Do you experience dryness of the nose, mouth, throat, chest or vagina?

Never Sometimes Often Constantly

13. Do you suffer from thyroid abnormality?

Yes No Uncertain

14. Are you known to sleep with your eyes partly open?

Yes No Sometimes

15. **Do you have eye irritation as you wake from sleep?**

Yes No Sometimes

Appendix 1. McMonnies questionnaire

1.2.6. Management and treatment

Therapy of dry eye requires a multifaceted approach including tear conservation, and tear replacement through methods such as punctum plug, novel anti-inflammatory drugs and surgical procedures (punctal occlusion, salivary gland transplantation, tarsorrhaphy and botulinum toxin induced ptosis) [82]. As evident from pathophysiology of dry eye, many factors contribute to or exacerbate dry eye, including: tear deficiency, tear instability, irritation and inflammation. Over the past few years, as a result of numerous studies, new concepts of pathogenesis have shown that DED seems to be inflammatory in origin, mediated by T-cell lymphocytes [85, 86]. This finding has also been augmented by the studies investigating the role of anti-inflammatory therapies. So, in the last few years, there has been a paradigm shift in the strategy to treat DED. However, conventional treatment still has importance.

1.3. Background and purpose of our studies

Keratoconus has well-described clinical signs, but early forms of the disease may be undiagnosed unless the corneal topography is studied. About 20 years ago Wilson and Klyce described that computer assisted topography analysis is a more sensitive tool in early diagnosis of keratoconus than keratometry or keratoscopy [87-92]. Since then, different corneal topographers have been developed and are in clinical use. The topographers provide different mathematical indices such as the Klyce/Maeda or Rabinowitz indices to determine the presence/absence of keratoconus. It is well known, that surface regularity (SRI) and surface asymmetry (SAI) indices may also exceed the normal range in keratoconus patients [93].
However, De Paiva et al. reported that SRI and SAI may also base the potential to be used as objective diagnostic indices for dry eye disease, as well as means to evaluate the severity of this disease [94].

The purpose of our first study was to determine the interaction between corneal tomographic parameters and dry eye disease in keratoconus (KC) patients [95].

Corneal thickness is decisive in case of planning a cross-linking treatment (corneal thickness should not be less than 400 μm) or implantation of intracorneal ring segments.
The second aim of our study was to assess whether Scheimpflug topographers and noncontact endothelial microscopes are able to measure appropriately corneal thickness in eyes with keratoconus and whether these values could be used interchangeably.

2. PATIENTS AND METHODS

Seventy-seven eyes of 49 patients with keratoconus (11 females and 38 males) aged between 18 and 62 years (mean age: 34.4 ± 11.6 years) were recruited from the Department of Ophthalmology, Saarland University Medical Center from October 2010 to March 2011. All measurements were performed by one examiner [95] (EZ). Informed consent about the procedures was obtained from all subjects and all the examinations followed the Tenets of the Declaration of Helsinki.

Keratoconus was diagnosed based on clinical and topographic evaluations. Subjects with previous history of ocular surgery or contact lens wear were excluded from the study. There were patients with keratoconus grade 1-4 according to Pentacam grading (Pentacam HR, Oculus, Germany), which has been adapted to classical Amsler or Muckenhirn-stages. Patients were grouped into grades 1+2 (mild KC) and 3+4 (severe KC).

In 77 KC eyes ophthalmic examinations consisted of best-corrected visual acuity measurements, slit-lamp examination, corneal tomography, corneal pachymetry, McMonnies and Schirmer tests, tear film break-up time (BUT) and in 26 KC eyes of additional high-speed video-topography.

The instruments used for corneal tomography were the Topographic Modeling System (TMS-5, Tomey, Tennenlohe, Germany) and the Pentacam (Pentacam HR, Oculus, Germany). The topographic parameters analyzed were surface regularity index (SRI), surface asymmetry index (SAI) and Klyce/Maeda keratoconus index (KCI) of TMS-5 and Index of Surface Variance (ISV), Index of Vertical Asymmetry (IVA), Keratoconus Index (KI), Center Keratoconus Index (CKI), Index of Height Asymmetry (IHA) and Index of Height Decentration (IHD) values of Pentacam.

The pachymetric parameters analyzed with both Scheimpflug systems were central corneal thickness (CCT), cone apex (CAT) and thinnest point thickness (TPT).

High-speed video-topography was performed in 10 eyes with mild and in 16 eyes with severe keratoconus, as detailed below.

2.1. Corneal topographic indices of TMS-5

The ***Surface Regularity Index*** (SRI) describes the topography of the central part of the cornea within the central 4.5 mm diameter. The power of each point is compared with the adjacent points. The calculation is based on the determination of the most frequently occurring axial power representation and the comparative analysis of dioptric powers of adjacent points in 256 hemi-meridians in the 10 central rings. An SRI value < 1.01 is considered normal (regular shape), while values above 1.97 are abnormal (irregular shape).

The ***Surface Asymmetry Index*** (SAI) is determined from the centrally weighted summation of differences in corneal power between corresponding points 180 degrees apart over the 128 equally spaced meridians. Low SRI and SAI values correspond to a more regular surface [90]. Normal corneas have a fairly symmetric power distribution (SAI < 0.5).

Within the ***Klyce–Maeda Indices***, KPI is the "keratoconus prediction index", which is derived from 8 quantitative videokeratography-derived indices (Simulated Keratometry (SimK1, SimK2), SAI, Differential Sector Index (DSI), Opposite Sector Index (OSI), Centre-Surround Index (CSI), Irregular Astigmatism Index (IAI) and Analysed Area (AA)). The method for calculating this index has been described earlier [40]. Maeda and co-authors suggested that a value larger than 0.23 indicate keratoconus.

KCI is derived using a binary decision-making tree that had input from the KPI (keratoconus prediction index) and 4 other indices (DSI, OSI, CSI and SimK2), described by Klyce and Maeda. The degree of the keratoconus-like pattern is determined and expressed as a percentage, which is the KCI%. Maeda and co-authors [40, 96] suggest that a value greater than zero is indicative of keratoconus.

2.2. Corneal pachymetric parameters

The instruments used for corneal pachymetry were the Topographic Modeling System (TMS-5, Tomey, Nagoya, Japan) with dual Placido and Scheimpflug imaging, the Pentacam Scheimpflug imaging (Pentacam HR, Oculus, Germany) and noncontact specular microscopy (EM-3000, Tomey, Nagoya, Japan).

The dual Scheimpflug analyzer provides corneal thickness measurements for the central 9.0 mm zone. Data are automatically recorded in concentric rings (with a diameter of 1.0 mm, 3.0 mm and 4 mm related to the corneal center). The instrument shows the average CCT (referring to the central 4.0 mm of the cornea) and thinnest CCT.

CCT was also determined using noncontact specular microscopy (EM-3000). Patient's head was positioned in the chin rest and the patient was instructed to look straight focusing the fixation target. Auto mode low flash intensity pictures from the center of the cornea were taken. Among different parameters, the CCT could be extracted from these images.

The Pentacam takes a series of Scheimpflug images by rotating the gantry including slit and camera. From these slit images the diffuse volume scattering is analyzed and corneal thickness is extracted. The EM-3000 evaluated the mechanical movement of the imaging objective between focusing to the epithelium and the endothelium.

The pachymetric parameters analyzed with both Scheimpflug systems were central corneal thickness (CCT), cone apex and thinnest point thickness. The noncontact specular microscope EM-3000 measured central corneal thickness value (CCT).

2.3. Tear film parameters

The standard tear film break-up time (BUT) was evaluated using a slit-lamp microscope with a cobalt-blue filter. Fluorescein eye drops were instilled in the conjunctival sac of the patients. The subjects were then instructed to blink several times for a few seconds to ensure adequate distribution of fluorescein. The interval between the last complete blink and the appearance of the first corneal black spot in the stained tear film was measured. A BUT value of <10 seconds was considered abnormal [96].

Tear production was assessed using Schirmer's test without topical anaesthesia. The standardized strips of filter paper were placed in the lateral canthus away from the cornea and left in place for 5 minutes with the eyes closed. Readings were reported in millimeters of wetting within 5 minutes. A reading of < 5 mm was referred to the diagnosis of dry eye disease.

All patients were interviewed by McMonnies questionnaire, which includes 14 questions that focus on clinical "risk factors" for dry eye. The index score can range from 0 to 45. Values greater then 14.5 indicate dry eye disease based on previous sensitivity and specificity estimates [97].

Our high-speed video-topography system represents a novel sensor design.

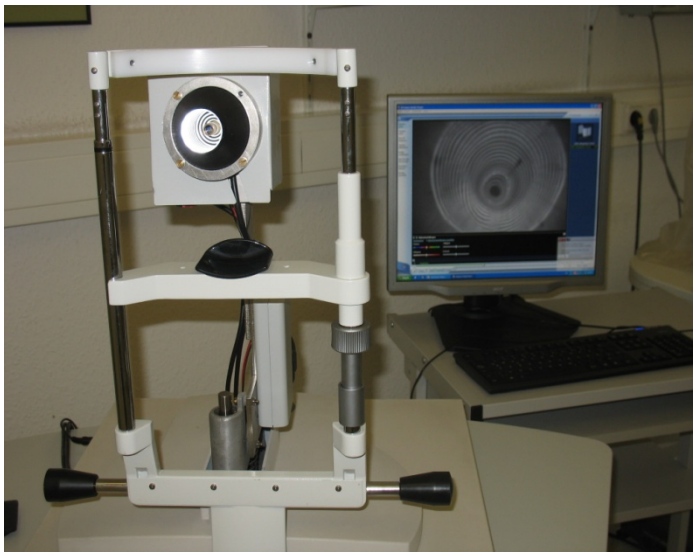

Figure 1. High- speed videotopographer (Tear Inspect).

Our system (**Figure 1)** is able to simultaneously analyze the tear film behavior with respect to its three different layers (mucin, liquid, and lipid) and the lipid layer in detail. Two CMOS-cameras (complementary metal oxide semiconductor) (IDS, Obersulm, Germany, UI-1548LE-M) were integrated in the sensor to measure the temporal progression of the tear film, each focusing at a different focal plane (**Figure 2**). Capturing the virtual image of a Placido grid (PG) reflected off the tear film, the first camera follows the principle of videokeratoscopy [98], while the second camera targets the lipid layer and, therefore, is focused on the anterior corneal surface. Depending mainly on the liquid layer, changes in the tear film over time lead to visible change in the virtual image of the PG [99].

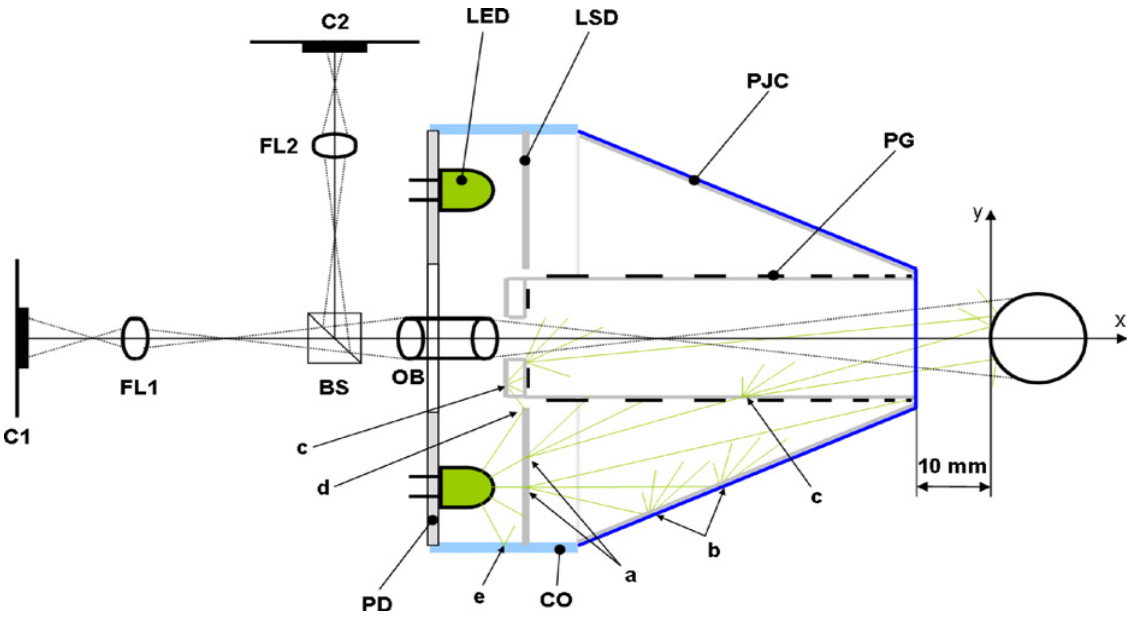

Figure 2. Principle drawing of the sensor. Light from LEDs is diffused by the LSD and propagates into the PJC. Homogeneous illumination is achieved by multiple reflection and scattering (green lines). PG is reflected off the anterior surface of the eye. Virtual image of PG and the lipid layer are focused on camera C1 and C2, respectively, by means of OB, BS and corresponding FL (dotted lines). LED: light emitting diodes; LSD: light shaping diffuser; PJC: projection cone; PG: Placido grid; PD: plastic disc; CO: Cover; OB: objective; BS: beam splitter; FL1/FL2: focusing lenses; C1/C2: cameras a/b/c: diffuse light scattering; d/e: specular light reflection [99].

Centration was performed first; then between two complete blinks a video was recorded. Each subject was asked to avoid head movements and to fixate the target light continuously during

the examination. The recorded videos were later analysed. The outcome measures selected for analysis were time of first irregularities of Placido rings (TIP), time of eyelid closure (TEC), presence of fat and direction of fat movement.

2.4. Statistical analysis

For statistical analysis of the data SPSS (SPSS release 17, IBM, USA) was used.

Nonparametric Mann-Whitney test was performed to compare numerical data of mild and severe keratoconus groups. To compare McMonnies questionnaire, Schirmer test and BUT positivity in mild and severe KC groups the Chi-Square test was used.

Spearman test was used to determine the correlation between the confounders mild and severe stage KC and tear function parameters and to define the correlation between the co-variables SAI, SRI, KCI of TMS-5 as well as ISV, IVA, KI, CKI, IHA and IHD of Pentacam and tear function parameters. Pearson test was performed to analyse the correlation between age and topographic or tear film parameters.

Corneal pachymetric data were documented with mean and standard deviation, correlation between variables was done using the Pearson test. Comparisons between variables were performed using non-parametric test (Wilcoxon). P-values less than 0.05 were considered statistically significant.

3. RESULTS

3.1.Demographic data

Of the 49 keratoconus patients, 11 were women and 38 were men. There were: 8 eyes (10.4%) with keratoconus grade 1, 25 eyes (32.5%) with grade 2, 26 eyes (33.8%) and 18 eyes (23.4%) with grade 3 and 4.

Keratoconus patients were subdivided into mild (grade 1-2) and severe stage (grade 3-4) groups using Pentacam grading. **Table 3** describes the demographic parameters for both keratoconus groups. There were no statistical significant differences concerning demographic data between mild (MKC) and severe stage KC patients (SKC).

Group	N	Mean ± SD (years)	Male (%)	Mean SEQ ± SD (Dptr)
Mild KC	33	32 ± 12	69.7	1.9 ± 4.2
Severe KC	44	30 ± 12.1	72.7	5.8 ± 5.3

Table 3. Demographic parameters of keratoconus (KC) patients (Mean ± SD).

Mild KC = KC stages 1+2; severe KC = KC stages 3+4; SEQ - spherical equivalent of refraction.

3.2. Topographic data

TMS-5

Using corneal tomography system (TMS-5), mean SRI, SAI, KCI values in MKC group were 0.56 ± 0.5 (Mean ± SD), 1.47 ± 0.8, 51.9 ± 30.8 compared to 1.36 ± 0.5, 2.89 ± 1.4 and 95.0 ± 28.8 in SKC group (**Figure 3**). All parameters were significantly higher in SKC compared to MKC ($P < 0.001$ for all parameters).

Pentacam

Using Pentacam, mean ISV, IVA, KI, CKI, IHA and IHD values were in MKC group 59.86 ± 15.24, 0.67 ± 0.21, 1.13 ± 0.06, 1.01 ± 0.03, 23.51 ± 19.84 and 0.05 ± 0.02 compared to 127.16 ± 34.15, 1.34 ± 0.38, 1.35 ± 0.13, 1.09 ± 0.07, 35.73 ± 26.62 and 0.14 ± 0.05 in SKC group. The differences between MKC and SKC groups were statistically significant (P < 0.001 for all parameters).

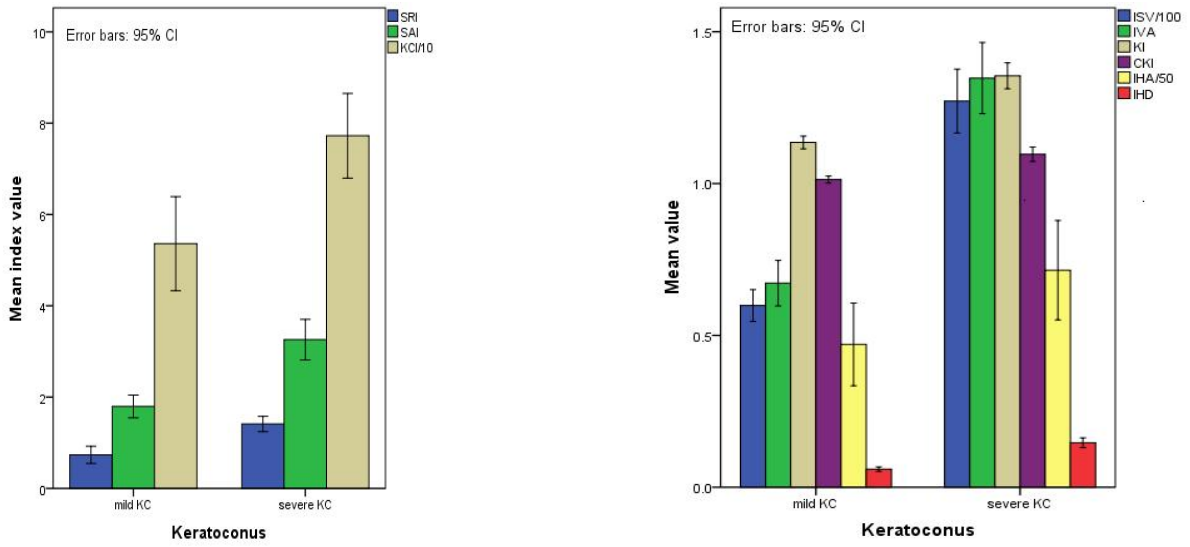

Figure 3. Changes of corneal topographic parameters with progression of keratoconus (KC).

SRI = surface regularity index; SAI = surface asymmetry index; KCI = Klyce/Maeda keratoconus index.

The differences between mild and severe keratoconus groups were statistically significant (P = 0.001 for all parameters), all indices were higher in severe stage keratoconus.

3.3. Pachymetric data

Table 4. Displays all pachymetric readings of our patients.

	Mild KC group			Severe KC group		
	CCT (μm)	CAT (μm)	TPT(μm)	CCT (μm)	CAT(μm)	TPT(μm)
TMS-5	505.0 ± 31.7	517.0 ± 44.1	498.0 ± 42.6	473.0 ± 24.9	473.0 ± 50.7	453.0 ± 60.0
Pentacam	504.0 ± 33.5	503.0 ± 36.5	486.0 ± 36.6	478.5 ± 36.3	460.5 ± 37.9	442.0 ± 53.8
EM-3000	482.0 ± 44.2	-	-	449.0 ± 89.4	-	-
P-values	$P^{*} = 0.0001$	$P^{*} = 0.005$	$P^{*} = 0.004$	$P^{*} = 0.0001$	$P^{*} = 0.001$	$P^{*} = 0.008$
	$P^{\#} = 0.0001$			$P^{\#} = 0.0001$		
	$P^{\Delta} = 0.0001$			$P^{\Delta} = 0.0001$		

Table 4. Pachymetric values (μm) with the dual mode (Placido and Scheimpflug) Topographic Modeling System TMS-5 (Tomey, Nagoya, Japan), Pentacam Scheimpflug imaging (Pentacam HR, Oculus, Germany), and noncontact specular microscopy (EM-3000, Tomey, Nagoya, Japan) in both keratoconus groups.

CCT = Central corneal thickness; CAT = cone apex thickness; TPT = thinnest point thickness.

P^{*} - values compare TMS-5 and Pentacam variables (Wilcoxon - test)

$P^{\#}$ - values compare TMS-5 and EM-3000 variables (Wilcoxon - test)

P^{Δ} - values compare Pentacam and EM-3000 variables (Wilcoxon - test)

Mean CAT using TMS-5 was 517.0 ± 44.1 μm in mild keratoconus group and 473.0 ± 50.7 μm in severe keratoconus group. Mean TPT was 498.0 ± 42.6 μm and 453.0 ± 60.0 μm, respectively. In mild keratoconus, mean central corneal thickness using Pentacam HR was 504.0 ± 33.5 μm. EM-3000 CCT in this group was lower (482.0 ± 44.2 μm) compared to values of Scheimpflug imaging. Difference between CCT measured with Pentacam HR and EM-3000 in severe keratoconus patients (478.5 ± 36.3 μm and 449.0 ± 89.4 μm) was much higher than the respevtive difference in mild keratoconus (**Table 4**).

There was a significant difference in both groups of keratoconus between CCT measured using Scheimpflug systems and EM-3000 (P = 0.001, Wilcoxon test) and between CAT and TPT using Pentacam and TMS-5 (P = 0.008 for all, Wilcoxon test).

For mild and severe keratoconus there was a significant correlation between CCT measured using Pentacam and EM-3000 (R = 0.93, R = 0.72, P = 0.0001) (**Figure 4**). CAT ((R = 0.93, R = 0.85, P = 0.0001) (**Figure 5)**) as well as TPT ((R = 0.87, R = 0.94, P = 0.0001) (**Figure 6**)) correlated highly significantly between the two Scheimpflug imaging systems. But the regression line for both groups does not pass through the origin.

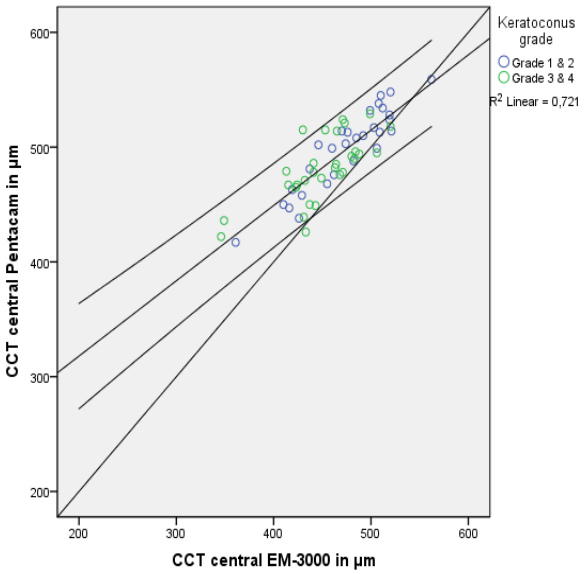

Figure 4. Correlation between CCT values measured using Pentacam and EM–3000 (y = 186.7 + 0.65·x).

CCT refers to central corneal thickness.

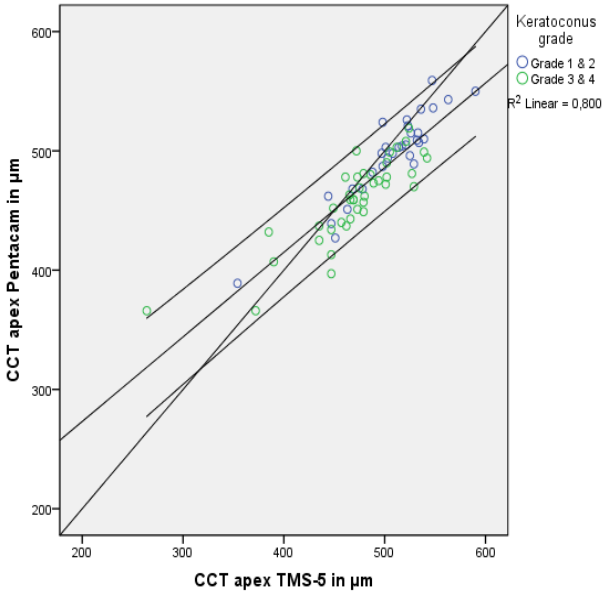

Figure 5. Correlation between CAT values using Pentacam and TMS–5 (y = 131.3 + 0.71·x).

CAT refers to cone apex thickness.

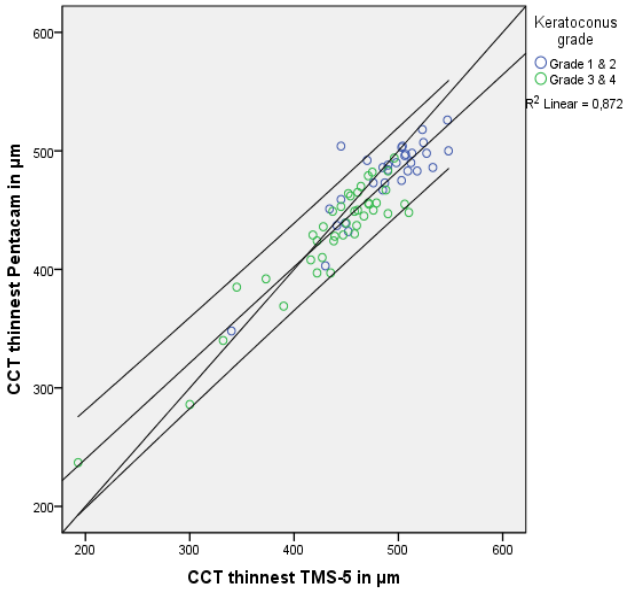

Figure 6. Correlation between TPT values using Pentacam and TMS–5 ($y = 77.7 + 0.81 \cdot x$).

TPT refers to the thinnest point thickness.

3.4. Tear film parameters

Tear film parameters are displayed at **Table 5**. Mean BUT was 8.5 ± 2.2 s in the mild and 8.0 ± 2.9 s in the severe keratoconus patients. There were 24 (73%) patients with BUT values lower then 10 s in mild keratoconus group and 33 (75%) patients in severe keratoconus group. The Schirmer test value averaged 22.0 ± 10.5 mm in patients with keratoconus grade 1 and 2 and 19.5 ± 11.4 in subjects with keratoconus grade 3 and 4. Only in 12 subjects (15.6% from all keratoconus patients) Schirmer test values were 5 mm or lower.

Mean McMonnies index was 10.0 ± 5.7 and 8.0 ± 6.7 in mild and severe keratoconus groups, respectively. Seventeen keratoconus patients (22%) were McMonnies positive (7 in mild and 10 in severe stage).

Mean TIP in mild keratoconus 8.3 ± 18.8 s, whereas it was 5.8 ± 18.8 s in severe keratoconus. For all subjects, first irregularities of Placido rings occurred at the apex of the cone, in the majority of cases in the temporal inferior quadrant **(Figure 7).** For mild KC, mean TEC was 17.2 ± 21.4 s and 16.1 ± 28.4 s in the severe KC groups. In both keratoconus groups, the lipid movement was bottom-up at the beginning and nasally directed before blinking (**Figure 8)**.

Group	BUT			McMonnies questionnaire			Schirmer Test			TIP	TEC
	Mean ± SD Time (s)	Positive (<10 s) N (%)	Total N (%)	Mean ±SD (points)	Positive (>14.5) N (%)	Total N (%)	Mean ±SD (mm)	Positive (<5 mm) N (%)	Total N (%)	Mean ± SD (s)	Mean ± SD (s)
Mild KC	8.5 ± 2.2	24 (73%)	33 (100%)	10.0 ± 5.7	7 (21%)	33 (100%)	22.0 ± 10.5	3 (9.1%)	33 (100%)	13.0 ± 18.8	25.8 ± 21.4
Severe KC	8.0 ± 2.9	33 (75%)	44 (100%)	8.0 ± 6.7	10 (22%)	44 (100%)	19.5 ± 11.4	9 (20.5%)	44 (100%)	12.5 ± 18.8	25.1 ± 28.4
P value	P* = 0.93	$P^{\#}$ = 0.82		P* = 0.82	$P^{\#}$ = 0.23		P* = 0.65	$P^{\#}$ = 1.00		P* = 0.66	P* = 0.69

TABLE 5. Tear function parameters in different stages of keratoconus (KC).

Legend: Mild KC = KC stages 1-2; severe KC = KC stages 3-4; BUT = break–up time; SRI = surface regularity index; SAI = surface asymmetry index; TIP = time of first irregularities of Placido rings; TEC = time of eyelid closure.

P* values compare mild and severe keratoconus groups (Mann-Whitney test).

$P^{\#}$ values compare mild and severe keratoconus groups (Chi-Square test).

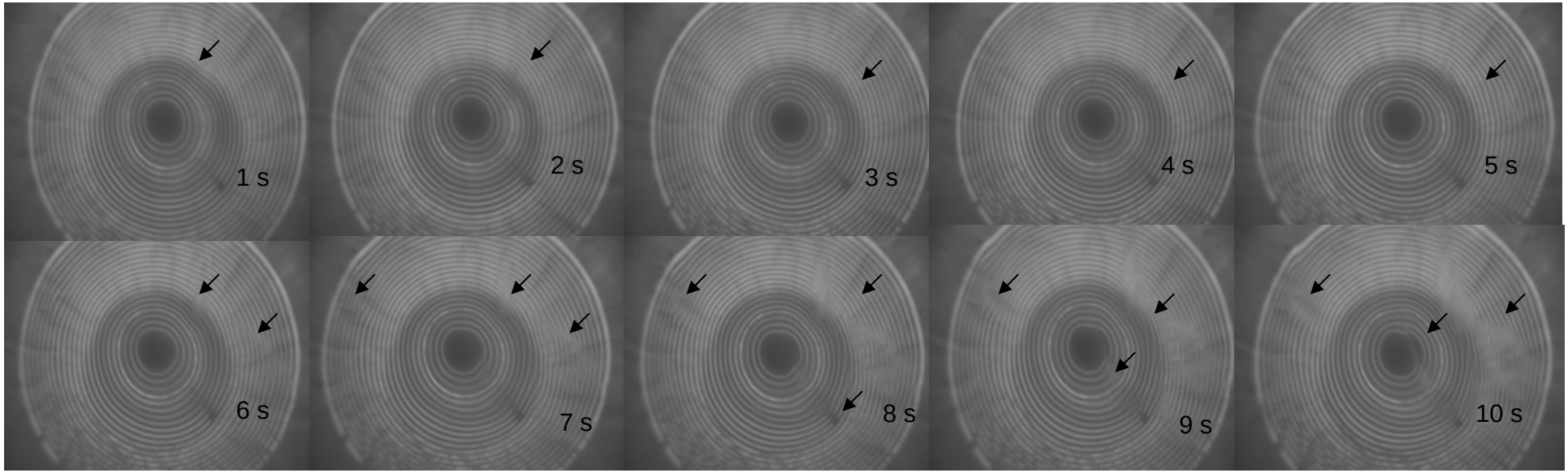

Figure 7. Changes of irregularities of Placido rings (TIP) during 10 seconds interblinking interval (Camera 1) in a patient with mild keratoconus.

TIP could be detected from the first second at the apex of the cone (see arrows). The first irregulatities were detected inferotemporally (note: due to hardware setting the camera image is rotated by 180 ˚).

Legend: TIP = time of first irregularities of Placido rings

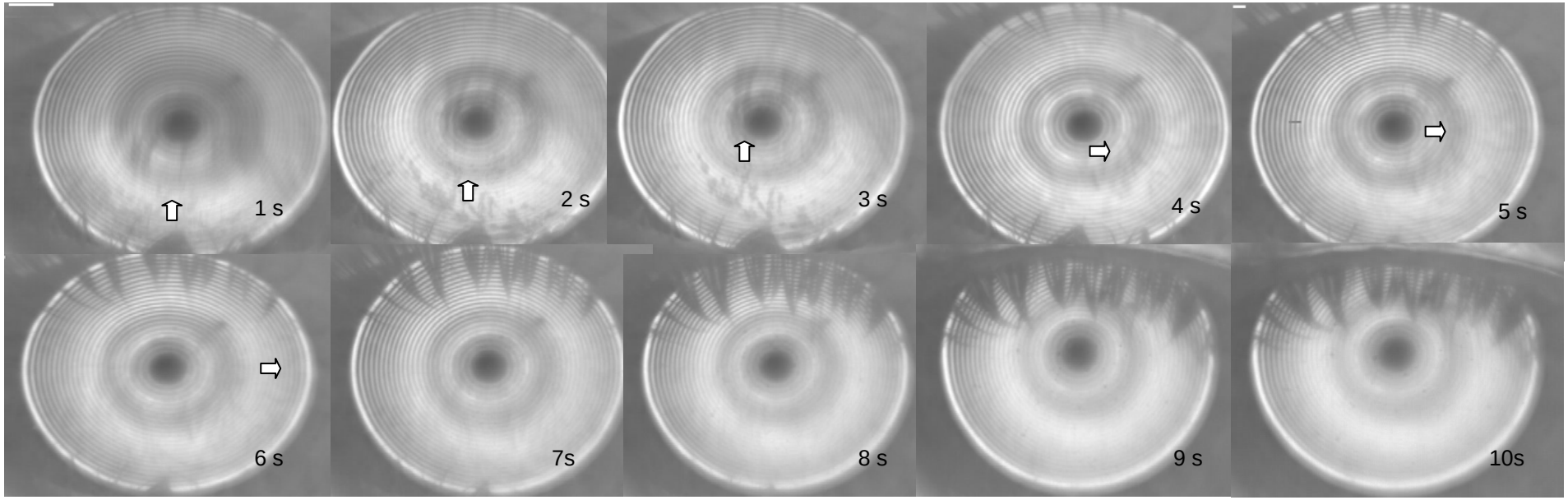

Figure 8. Changes of the lipid layer of tear film during 10 seconds interblinking interval (Camera 2) in a patient with keratoconus grade 1. From 1 - 3 s lipid movement is bottom-up, during 4 - 6 s temporonasally directed and from 7 - 10 seconds stable (see arrows).

There was no statistically significant difference between patients with mild and severe keratoconus concerning any of the examined tear film parameters ($P > 0.66$) [95].

There was neither significant correlation between keratoconus severity and tear film parameters nor between SRI, SAI, KCI of TMS-5 as well as ISV, IVA, KI, CKI, IHA, IHD of Pentacam and tear function parameters in the entire study group and in 44 SKC cases ($P > 0.16$) [95].

We detected a correlation between McMonnies index and age for all keratoconus patients ($r = 0.32$, $P < 0.001$), but none of the other tear film or topographic parameters was correlated with age [95].

4. DISCUSSION

4.1. Interaction of tear film and topographic parameters in keratoconus

Keratoconus (KC) was first described in detail in 1854 [1]. Despite the intensity of research activities over the last few decades into its aetiology and pathogenesis, the cause(s) and possible pathomechanisms for development of KC remain poorly understood. Several hypotheses propose genetic, environmental, biomechanical and biochemical causes and mechanisms.

In our project we focused on the relationship of corneal topography with tear film properties in keratoconus patients. The most conspiciuous finding of our study is that dry eye disease and topographic changes do not interact in keratoconus patients. There was no correlation between SRI, SAI, KCI, ISV, IVA, KI, CKI, IHA and IHD with any of the examined tear film parameters of keratoconus patients. In addition, there was also no significant difference between patients with mild and severe keratoconus concerning any of the examined tear film parameters ($P > 0.66$)[95].

In our study, mean BUT was 8.5 ± 2.2 s in MKC and 8.0 ± 2.9 s in SKC. Schirmer test values were 22.0 ± 10.5 mm and 19.5 ± 11.4 mm, respectively. This is in contrast to the results of previous study of Dogru et al.[100], who detected lower BUT and Schirmer test values in keratoconus patients (also without previous contact lens wear) compared to our results. The difference between both studies may be explained by different study populations. Dogru et al. used the central corneal power and radius of curvature to grade keratoconus patients into mild, moderate and severe groups. We used Pentacam grading and patients were subdivided into mild (grade 1-2) and severe stage (grade 3-4) keratoconus groups. However, the age of our examined patients was similar to that of Dogru et al., the gender distribution was different. In the keratoconus group by Dogru et al. there were 16 females (41% of all keratoconus patients) while in our study there were only 11 females (22% of all keratoconus patients). Unlike our

study the latter study was performed in Turkey, where the air temperature and humidity are higher as compared to Germany. Wolkoff et al. [71] have shown that higher air temperature and humidity and the use of air-conditioning systems may worsen eye irritation symptoms and tear film stability.

Dogru et al. [(99)] described, that the ocular surface disease in keratoconus is characterised by disorder of tear quality, squamous metaplasia and goblet cell loss, all of which seem to be related to the extent of keratoconus progression. In our study, we could not verify correlation of tear film parameters and topographic progression of keratoconus disease. As expected, in MKC and SKC patients, SAI and KCI values were elevated. Nevertheless, in severe keratoconus patients we could not find correlation between corneal topographic indices and tear film parameters. Thus, we may assume that corneal topographic changes are not related to tear film dysfunction in keratoconus.

In our study more than 20% of keratoconus patients were diagnosed as dry eye patients. The prevalence of dry eye from large epidemiological studies reveals a range of about 5% to over 35% at various ages [(57)]. Dogru and Tsubota reported, that healthy patients aged ≥ 50 years usually first present dry eye [(18)]. In our study, the mean age of keratoconus patients with dry eye disease was 40.8 years (McMonnies positive), about one decade earlier than reported in healthy subjects. McMonnies index of keratoconus patients was correlated with age, which shows that similar to a normal population, dry eye disease progresses with age in keratoconus. We suggest, that ophthalmologists should analyse dry eye symptoms of keratoconus patients, as prevalence of dry eye is higher in keratoconus patients than in the normal population and may even be underdiagnosed.

De Paiva et al. [(10)] suggested that SAI and SRI may have the potential to be used as objective diagnostic indices for dry eye disease, as well as to evaluate the severity of dry eye disease. They described that chronic ocular desiccation and aqueous tear deficiency may produce

inferior corneal steepening in topography analysis and high astigmatism mimicking keratoconus. We could clarify that in keratoconus patients SAI and SRI are inappropriate to be used as indicators for dry eye and we could not determine an impact of dry eye disease on anterior corneal topographic parameters of keratoconus patients.

In conclusion, there is no interaction between dry eye disease and tomographic changes of keratoconus patients. Tear film parameters of keratoconus patients have to be analysed more in detail in the future [95].

4.2. Pachymetric readings in keratoconus

Currently, Placido–disk-based corneal topography is regarded as the most sensitive measurement for detecting ectatic corneal disorders such as keratoconus [8, 23, 89, 101-103]. Topographic analyses have revealed characteristic features of this disease before biomicroscopic signs or symptoms [9, 104]. Normal, suspicious, and abnormal topography patterns of this disease have been classified [105-108]. Quantitative topographic indices, such as the Rabinowitz index (Rabinowitz 1995), keratometry, and mean curvature [44, 109, 110] have been developed to diagnose keratoconus [1, 41, 111, 112]. However, topography screening methods have shortcomings. First, satisfactory topographic measurement may be not available due to corneal irregularity or tear film breakup. Second, topography may not detect all patients at risk for keratectasia. Randleman et al. [113] reported a meta-analysis in which 27% of 93 postrefractive surgery ectasia cases showed normal preoperative topography, and 22% have an equivocal pattern. Third, it is difficult for these topography-based methods to distinguish keratoconus from contact lens-induced warpage, subepithelial deposits or scarring, tear film abnormalities, lid artifact, or other causes of corneal distortion 114-116. These reasons for topographic distortion may cause a false-positive diagnosis of keratoconus or mask a true diagnosis of keratoconus.

Corneal thinning is a key pathologic feature of keratoconus 9; therefore, a keratoconus diagnosis based on corneal thickness measurement may offer additional information not available on topography 117.

Our pachymetric data indicate that both measurement techniques using Scheimpflug imaging yield higher values for corneal thickness compared to specular microscopy, more pronounced for severe form of keratoconus and less for the mild form. There might be different reasons for that finding:

First, Scheimpflug imaging is based on an oblique projection of a slit maintaining the Scheimpflug condition, that means, that the intersection of a slit image with the front and the back surface takes place at different lateral positions and the front and back surface geometry has to be derived from the global shape extracted from a full set of Scheimpflug images. One single image cannot provide sufficient information about corneal thickness. In contrast, specular microscopy uses comparably small incident angles of the incident ray and the light detection pathway and therefore one focal measurement may yield sufficient data for corneal pachymetry.

Second, Scheimpflug imaging uses wide field imaging for the slit projection technique. That means, that a slit size of more than 8 mm is projected to the cornea. Even if the front surface of the cornea is directly measured geometrically, the back surface and all deeper structures of the eye are not. They are imaged through all superficial refracting surfaces, in other words the corneal back surface is an image through the corneal front surface. To get real geometrical data, the back surface has to be inversely raytraced through the corneal front surface, and therefore, the front surface data as well as the (virtual, non-geometric) back surface structure have to be fitted by a model surface to apply raytracing techniques. Most of the Scheimpflug based topographers use simple floating spheres or rotationally symmetric aspheres for characterizing these refracting surfaces. Especially in cases with keratoconus, where the

global fitting algorithms may lack due to focal ectasia of the cornea, inverse raytracing does no longer provide real geometrical data of the corneal back surface and therefore Scheimpflug techniques might be inaccurate.

Third, in keratoconus the true front and back surface geometry might not be parallel at the corneal apex as it is in normal corneas. In contrast, if corneal steepening associated with corneal ectasia occurs in the lower temporal quadrant, this condition of parallel corneal front and back surface might be valid in the region of the cone apex. As specular microscopy systematically searches for parallel behavior of both corneal surfaces, the measurement might not take place at the corneal center as it is in normal situations, but at the cone apex or the thinnest point of the cornea. This fact is interesting, because up to our knowledge, it was not published up to now that specular microscopy does not consequently measure central corneal thickness, but yields proper images of the corneal endothelium if both corneal surfaces are locally parallel, which is disjunctive to corneal center in diseases such as keratoconus. In our study, we found that the EM-3000 pachymetric data (so called CCT-data) are very close to the CAT and TPT data measured with both Scheimpflug imaging techniques and correlate well ($P < 0.001$) with exception of CAT of the TMS-5 ($P = 0.02$ for mild and $P = 0.04$ for advanced keratoconus). This exception might be explained by the fact, that the TMS-5 is up to our knowledge the only Scheimpflug system on the market which fits a 2 dimensional polynomial of 5th degree to the detected edges of the front and back surface for inverse raytracing and therefore is a more individual and advanced model even for irregular surface structures such as in keratoconus.

In conclusion, several corneal instruments are available to measure corneal thickness with varying degrees of accuracy. In our study we showed, that central corneal thickness, cone apex and thinnest point thickness measurements using Scheimpflug imaging and noncontact

specular microscopy should not be used interchangeably in mild and in a progressed stage of keratoconus, but could be transferred using linear regression. This might be important in case of surgery planning, e.g. for crosslinking treatment or intracorneal rings, where a sufficient corneal thickness is mandatory.

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6. PUBLICATIONS AND CONFERENCE PARTICIPATIONS

Scientific publications:

Zemova E, Eppig T, Stefan A, Seitz B, Toropygin S, Langenbucher A, Szentmáry N. Correlation between topographic parameters and dry eye disease in keratoconus patients. *Curr Eye Res 2012; Revision submitted.*

Zemova E, Akova Budak B, Eppig T, Seitz B, Toropygin S, Szentmáry N, Langenbucher A. Comparison of corneal thickness measurements using Scheimpflug imaging, corneal topography and noncontact specular microscopy in keratoconus eyes. *In preparation.*

Scientific presentations:

1. Zemova E, Eppig T, Stefan A, Seitz B, Toropygin S, Langenbucher A, Szentmáry N. Correlation between topographic parameters and dry eye disease in keratoconus patients. 2nd EuCornea Congress, European Society of Cornea & Ocular Surface Disease Specialists. Vienna, Austria, 16.09-17.09.2011

2. Zemova E, Eppig T, Stefan A, Seitz B, Toropygin S, Langenbucher A, Szentmáry N. Dry eye syndrome in keratoconus patients. 109. Kongress der Deutschen Ophthalmologischen Gesellschaft (DOG), Berlin, Germany, 29.09-2.10.2011

3. Zemova E, Akova Budak B, Eppig T, Seitz B, Toropygin S, Szentmáry N, Langenbucher A. Comparison of corneal thickness measurements using Scheimpflug imaging, corneal topography and noncontact specular microscopy in keratoconus eyes. 109. Kongress der Deutschen Ophthalmologischen Gesellschaft (DOG), Berlin, Germany, 29.09-2.10.2011

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