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• Review Article •

Corneal and intraocular pressure changes associated to the circadian rhythms: a narrative review

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Abstract
● **AIM:** To synthesize the current body of research regarding the diurnal variations in intraocular pressure (IOP) and corneal biomechanical and morphological parameters, highlighting their significance in various eye conditions.

● **METHODS:** A comprehensive review of studies on the diurnal variations of IOP and corneal parameters was conducted. Tonometry findings from various studies were assessed, including the Goldmann applanation tonometry (GAT) and non-contact tonometers. Data on the variations in central corneal thickness (CCT), corneal curvature, and corneal biomechanics measured by the Ocular Response Analyzer system across different population groups was extracted and analyzed.

● **RESULTS:** In both healthy subjects and those with Fuchs dystrophy, IOP and CCT demonstrate marked diurnal declines. GAT remains the gold standard for tonometry, with the highest reliability. However, its measurements are influenced by CCT. Keratoconus patients and those with pseudoexfoliation showed significant diurnal variations in IOP. The biomechanical parameters, especially corneal hysteresis (CH) and the corneal resistance factor (CRF), largely remain stable throughout the day for most of eye conditions, with some exceptions. Notably, the corneal morphology diurnal variation, particularly curvature, yielded mixed conclusions across studies.

● **CONCLUSION:** Circadian rhythms significantly influence various corneal parameters, most notably IOP and CCT. Further studies should emphasize standardized approaches larger sample sizes, and delve deeper into less-explored areas, such as the effects of orthokeratology lenses on diurnal biomechanical shifts.

● **KEYWORDS:** circadian rhythms; intraocular pressure; corneal thickness; corneal biomechanics; corneal curvature
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INTRODUCTION

Corneal biomechanics studies how the cornea behaves when it is exposed to diverse forces. A cornea with proper biomechanical properties can maintain its correct morphology as it becomes stable as well as it physiological function, including transparency[1]. It also plays an instrumental role in the understanding and diagnosis of various eye diseases, such as keratoconus, glaucoma, and corneal dystrophies[2-6]. Systemic conditions like diabetes also correlate with corneal biomechanical alterations[7]. When discussing corneal biomechanics, references are often made to changes induced mechanically, arising from biological stimuli. A notable illustration of its importance is keratoconus, where the weakening of corneal collagen structures leads to visual impairments[5]. Early diagnosis of keratoconus would significantly benefit from recognizing biomechanical changes during its preclinical phase[8].

Furthermore, understanding the biomechanical properties of the cornea aids in the success of treatments such as the fitting of orthokeratology lenses, as it is highly dependent on corneal biomechanics[9-10]. The results obtained with orthokeratology lenses will differ depending on the mechanical or morphological parameters of the cornea, with a worse response to the treatment of cases with flatter corneas or lower corneal stiffness[10]. Several corneal surgeries aim to enhance the resistance of the cornea or to mold the corneal shape, like corneal collagen crosslinking or the implantation of intrastromal corneal ring segments[11], in which the preoperative biomechanical status of the cornea is something essential for the surgical outcome. Currently, direct clinical measurements of these properties are not available. Although designed to measure the intraocular pressure (IOP), non-contact tonometers like the Ocular Response Analyzer (ORA; Reichert Ophthalmic Instruments, Buffalo, NY, USA) and CorVis ST (Oculus Optikgërate, Wetzlar, Germany) present indirect methodologies to assess corneal biomechanics. The ORA applies a rapid air pulse to alter corneal curvature, which is then analyzed to deduce parameters like the corneal compensated IOP (IOPcc), the Goldmann correlated IOP (IOPg), corneal hysteresis (CH), and the corneal resistance factor (CRF)[12-13]. CH is calculated as the difference in IOP between the first and the second corneal applanation during the air pulse, and the CRF depends on the IOP and the corneal thickness. Although these parameters can be considered as indirect biomechanical measures, only CH is said to be indirectly related to corneal viscoelasticity. CorVis ST also provides indirect measures of corneal biomechanics, being most of them highly influenced by corneal thickness[14].

Another layer of complexity arises from factors such as circadian rhythms and sclera-conjunctival morphology. Their understanding assists clinicians in tailoring appointment schedules and interventions, especially when considering how these rhythms influence ocular functions—critical for surgical planning. Circadian rhythms influence numerous ocular pathologies. Factors like night exposure to short-wavelength light from electronic devices exacerbate sleep disturbances[15] or promoting dry eye syndrome[16], with longer sleep durations increasing diabetic retinopathy risks and shorter durations heightening cataract risks[17]. These rhythms also affect clinical treatments, such as orthokeratology lens adaptations[14].

While biomechanical changes in the cornea present themselves across various diseases, distinguishing these changes—intrasubject variations, intra-measurement discrepancies, or circadian influences—remains challenging. Consider, for instance, that decreased CH and CRF can indicate conditions like keratoconus, pseudoexfoliation, or Fuchs dystrophy[18-20], or the association between thinner central corneal thickness (CCT) and reduced CH to heightened glaucoma risk[21-22]. Recognizing the role of circadian rhythms is, therefore, paramount.

This narrative review seeks to elucidate the influence of circadian rhythms on corneal biomechanical and morphological parameters and IOP across a spectrum of subjects, from the healthy to subjects with glaucoma, keratoconus, pseudoexfoliation, Fuchs endothelial dystrophy, and orthokeratology lens wearers.

METHODS

Three bibliographic search engines were used for the review: Pubmed, Scopus, and Web of Science. The Mendeley Reference Manager (Elsevier) was used to collect a database of the relevant references. The review was performed on February 2023 and revised on March 2024. Inclusion criteria for the review were: 1) studies that measured daily variations in IOP, and in corneal biomechanical and morphological properties (thickness and curvature), 2) articles published between the years 2000 and 2023, 3) Spanish or English as the publication language. Exclusion criteria were articles not meeting the inclusion criteria, case reports and animal experiments. There were no restrictions in terms of study design or sample size for the selection of the studies. This study was approved by the Ethics Committee of the University of Alicante (approval number: UA-2023-01-19_2).

The search equation used was the following: (circadian OR diurnal) AND (changes OR rhythms) AND (cornea*) AND (biomechanics OR "intraocular pressure" OR "thickness"). First, titles and abstracts were screened, duplicates were removed, and papers meeting the objective were selected for a full-text review. After this, the references within these selected papers were examined, leading to the inclusion of additional relevant articles that were missed in the initial search.

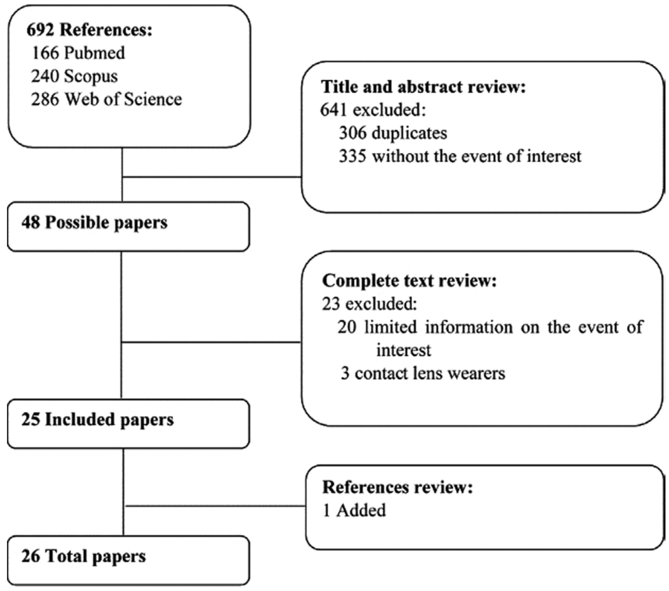

Figure 1 Flowchart showing the results obtained after the bibliographic review.

RESULTS

Six hundred and ninety-two (692) references were found among the three bibliographic search engines, from which 306 duplicates were removed, obtaining 386 references (Figure 1). Of those, 335 references were excluded after the title and abstract analysis for not meeting the inclusion criteria. Afterwards, the 48 resulting papers were analyzed for a complete text review, excluding 23 (20 for limited or incomplete information on the event of interest and 3 for using a sample of contact lens wearers). Finally, the references of the 25 papers included were analyzed, including one more article not found in the initial search.

Table 1 Summary of the major findings about diurnal variation of IOP of the articles included in this review

Author	Year	*n*	Subject type	Age (y)	Methods	Conclusion
Kóthy *et al*[23]	2001	7 (14 eyes)	POAG	53.8 (44-68)	GAT, ultrasound, self-tonometry	IOP and CCT decrease significantly throughout the day. IOP diurnal variation differs when using GAT and self-tonometry.
Fogagnolo *et al*[24]	2006	30	POAG	55-84	Perkins, GAT, ultrasound	There are no significant changes in IOP during the day. CCT varies significantly throughout the day, with the maximum peak at 4:00 and the minimum at 16:00.
Hamilton *et al*[25]	2007	25	Healthy	21.0±1.17 (18-23)	GAT, ultrasound	IOP and CCT decrease significantly throughout the day. The corneal curvature decreases significantly between 7:00 and 9:00, after which it remains stable.
Tajunisah *et al*[26]	2007	151 (302 eyes)	Healthy (*n*=50, 100 eyes); glaucoma suspect (*n*=101, 202 eyes)	Healthy: 49.25 (51-70); glaucoma suspect: 54.13 (34-89)	GAT	The maximum peak of IOP in healthy eyes occurs at 18:00-19:00, while in glaucomatous eyes occurs at 10:00-11:00. Eyes with suspected glaucoma (POAG, normal tension glaucoma, ocular hypertension, physiologic cup) have a more significant diurnal variation of IOP than healthy eyes.
Mosaed *et al*[27]	2008	81	Healthy (*n*=29); untreated glaucoma (*n*=52)	Healthy: 57.5±8.2 (40-74); glaucoma: 60.8±10.7 (40-79)	Pneumatonometer, ultrasound	There is no correlation between the diurnal variation of IOP and CCT. There is no difference in the variation of IOP and CCT throughout the day between healthy and untreated glaucoma subjects.
Read *et al*[28]	2008	15	Healthy	22 (20-27)	Optical biometer, dynamic contour tonometer	IOP and CCT decrease significantly throughout the day, with a maximum of 9:00 and 6:00, respectively.
Fogagnolo *et al*[29]	2010	40	Treated POAG (*n*=30); untreated POAG (*n*=10)	Treated: 55-84; untreated: 57-78	GAT, Perkins, ultrasound	IOP and CCT remain stable throughout the day. There is no difference between the variation of IOP and CCT between treated and untreated glaucoma subjects.
Syed *et al*[30]	2019	85	Pseudoexfoliation	62.51±8.9	GAT, ultrasound	IOP and CCT significantly decrease throughout the day in eyes with pseudoexfoliation, with the highest peak in the first measurement after awakening. There is a correlation between the diurnal variation of IOP and CCT.

POAG: Primary open angle glaucoma; CCT: Central corneal thickness; IOP: Intraocular pressure; GAT: Goldmann applanation tonometry.

The resulting papers were divided into two groups for their analysis: those that exclusively determined the impact of circadian cycles on IOP, which were summarized in Table 1[23-30], and those that analyze the impact on corneal biomechanics and morphology in Table 2[31-48].

Of the twenty-six studies analyzed, fourteen were conducted on healthy subjects, seven on glaucoma subjects, two on Fuchs dystrophy, one on eyes with pseudoexfoliation, one on keratoconus, and one on orthokeratology users. IOP and CCT increase overnight, reaching a maximum peak in the first morning hours for healthy and pseudoexfoliated eyes (Table 1). In glaucomatous eyes, this tendency needs to be clarified; there is more variability among studies.

The ORA is still the most popular instrument to assess biomechanical properties in these studies. Biomechanical parameters of the cornea, such as CH and CRF, are not highly affected by circadian rhythms in healthy and glaucomatous eyes (Table 2). On the other hand, there are mixed results on how corneal curvature is affected by circadian rhythms.

DISCUSSION

Intraocular Pressure For healthy subjects, the IOP measured with Goldmann applanation tonometry (GAT) decreases significantly throughout the day[25,40-41], with the change ranging between between 2.5 and 3.33 mm Hg[40,48]. Almost all the studies reported that the maximum peak in IOP occurs right after awakening, between 6.30 and 9.30[25,28,46]. Tajunisah *et al*[26] reported that the peak in IOP occurred between 18:00 and 19:00. Due to its lower variation coefficient (3.52%), GAT is considered the gold-standard for tonometry. Other tonometers, such as the ORA (11.06%-8.68% for IOPcc and IOPg, respectively) or the dynamic contour tonometer (7.18%) present a higher variation[26]. Therefore, a higher diurnal variability has been found in non-contact tonometers compared to GAT. As a downside, IOP measurements obtained with GAT rely on the Imbert-Fick law and, thus, are directly influenced by the CCT[49]: GAT can be overestimated in thick corneas and underestimated in thin corneas.

Glaucoma patients present a higher variability in the circadian cycle and IOP relationship. Tajunisah *et al*[26] studied differences in corneal circadian changes between subjects with suspected glaucoma and healthy subjects. They concluded that IOP presents a more significant diurnal change in subjects with primary open-angle glaucoma, normal tension glaucoma, ocular hypertension, or physiologic cup than healthy subjects[26]. Mosaed *et al*[27] determined no difference between the diurnal variation of IOP in untreated glaucoma patients and healthy eyes. Remarkably, there was no difference in the diurnal variation of IOP between treated and untreated glaucoma[29]. The maximum peak of IOP in subjects with glaucoma was found to be very similar to that obtained for

Table 2 Summary of the major findings about diurnal variation of corneal biomechanical and morphological parameters of the articles included in this review

Author	Year	*n*	Subject type	Age (y)	Methods	Parameters	Conclusion
Kida *et al*[31]	2006	15	Healthy	22.1±1.9 (20-25)	ORA, ultrasound	IOP, CCT, CH	IOP and CCT are higher during the night hours than during the day. There are no differences in CH throughout the day. The diurnal variation of IOP is not associated with corneal biomechanics.
Laiquzzaman *et al*[32]	2006	21 (42 eyes)	Healthy	39.8±12.2 (21-65)	ORA, ultrasound	IOP, CCT, CH	There is no significant diurnal variation in CH or CCT. IOP decreases significantly throughout the day.
Giráldez-Fernández *et al*[33]	2008	10	Healthy	-	Topography, videokeratoscopy	CCT, corneal curvature	CCT decreases significantly throughout the day, while corneal curvature presents its lowest value upon awakening but remains stable from this point on.
González-Méijome *et al*[34]	2008	58	Healthy	25±6 (19-45)	ORA	IOPg, IOPcc, CRF, CH	IOPg, IOPcc, CRF, and CH do not vary significantly throughout the day. Diurnal changes in IOPcc and IOPg are related to CH and CRF.
Shen *et al*[35]	2008	20	Healthy	19.7±1.1	ORA, OCT	IOPg, IOPcc, CRF, CH	CCT, IOPcc, IOPg, and CRF increase significantly from awakening throughout the day. There is no diurnal variation of CH.
Read *et al*[36]	2009	15	Healthy	22 (20-27)	Topography, optical biometer, DCT	CCT, corneal curvature	CCT is higher upon awakening and decreases throughout the day. The curvature of the anterior corneal surface flattens in the morning, while the posterior curves.
Kotecha *et al*[37]	2009	62	Healthy (*n*=26); untreated glaucoma (*n*=36)	Healthy: 62.3±11.4 (23.6-77.1); glaucoma: 57.2±13.8 (28.0-80.9)	ORA, optical low coherence reflectometry, GAT, DCT	IOP, CCT, CH	There are significant diurnal changes in CCT and IOP, being more lavish upon awakening. There are no diurnal changes in CH.
Oncel *et al*[38]	2009	62	Healthy	30.6±5.18	ORA, ultrasound	IOPg, IOPcc, CCT, CRF, CH	There is no significant difference in the biomechanical parameters (IOPg, IOPcc, CH, CRF, CCT) throughout the day.
Villas-Bôas *et al*[39]	2009	33 (62 eyes)	Healthy (*n*=12, 24 eyes); primary open angle glaucoma (*n*=21, 38 eyes)	Healthy: 43.0±13.3; glaucoma: 64.4±11.1	GAT, DCT, ORA, ultrasound	IOP, CCT, CH, CRF, central corneal radius	The maximum IOP in healthy and glaucomatous eyes occurs upon awakening, changing significantly throughout the day. Central corneal radius, CH, and CRF do not vary throughout the day. CCT increases throughout the day in eyes with glaucoma but not in healthy eyes.
Lau *et al*[40]	2012	25	Healthy	21.0±1.6	Keratometer, ORA, GAT, ultrasound	IOP, central corneal radius, CCT, CH, CRF	The diurnal variation of CCT and CRF is correlated with IOP. The variation of CCT is correlated with CH and CRF.
Hon *et al*[41]	2016	25	Healthy	23.0±1.0 (21-25)	Topography, GAT	IOP, CCT, central corneal radius, corneal tangent modulus, corneal stiffness	IOP and CCT decrease significantly during the day. Corneal curvature, tangential modulus, and stiffness remain stable throughout the day.
Burfield *et al*[42]	2018	42	Healthy	27.2±4.2 (22-41)	Spectral-domain OCT imaging, optical biometry	CCT	CCT varies significantly throughout the day. Diurnal changes are not significantly different between myopic and emmetropic eyes.
Fritz *et al*[43]	2019	55	Fuchs dystrophy (*n*=44); healthy (*n*=11)	Fuchs: 70 (64-77); healthy: 74 (64-77)	Topography	CCT, posterior curvature	In healthy eyes, the CCT remains stable throughout the day. In eyes with Fuchs dystrophy, CCT, and posterior corneal radius thin significantly during the first 4h after awakening, after which time they remain stable.
Loreck *et al*[44]	2020	51	Fuchs dystrophy (*n*=29); healthy (*n*=22)	Fuchs: 70.7±8.6; healthy: 58.9±17	Topography	CCT	In eyes with Fuchs dystrophy and healthy eyes, CCT is significantly higher upon awakening than in the afternoon. This variation is more significant in eyes with Fuchs dystrophy.
Çiçek *et al*[45]	2020	26	Keratoconus	30±8.8	GAT, topography	IOP, CCT, MCT, corneal curvature	IOP, CCT, and MCT decrease throughout the day. Corneal curvature does not show diurnal variation.
Chen *et al*[46]	2021	21	Healthy	24.2±1.6 (21-26)	OCT, micro air puff system	CCT, elastic modulus, IOP	There is no significant diurnal variation in the corneal modulus of elasticity, CCT, and IOP.
Pérez-Corral *et al*[47]	2023	75	Orthokeratology patients	18-62	Corvis-ST	CCT	There are significant differences in CCT between morning and afternoon after wearing orthokeratology one night and after one week and three months.
Biswas et *al*[48]	2023	60	Healthy	30±5	Swept source-OCT, ORA	CCT, IOPcc, IOPg, CH, CRF	The diurnal variation of CCT, anterior and posterior corneal power, CCT and IOPg is significant. The diurnal variation of IOPg is inversely related to the anterior corneal curvature.

ORA: Ocular Response Analyzer; CCT: Central corneal thickness; MCT: Minimum corneal thickness; IOP: Intraocular pressure; GAT: Goldmann applanation tonometry; DCT: Dynamic contour tonometer; CH: Corneal hysteresis; CRF: Corneal resistance factor; IOPcc: Corneal compensated intraocular pressure measured with the ORA system; IOPg: Goldman correlated intraocular pressure measured with the ORA system; OCT: Optical coherence tomography.

healthy subjects, occurring after awakening between 6:30 and 9:00[27,39].

Syed *et al*[30] determined that eyes with pseudoexfoliation presented a significant diurnal variation in the IOP when measured with GAT. Keratoconus patients also presented a significant diurnal variation in IOP measured with GAT, peaking at 9:00 and reaching a valley at 17:00[45].

According to the literature revised, patients with high risk of glaucoma need to control their IOP periodically, but considering the effects of diurnal variation as this parameter can vary significantly from visit to visit depending at what time was measured. To correctly measure this parameter at office or self-monitored, the measurements must be taken at the same time point during the day, as there can be some diurnal variation that can lead to wrong conclusions and then wrong clinical decisions.

Central and Peripheral Corneal Thickness In healthy subjects, CCT increases during sleep hours and decreases during wake hours, peaking right after awakening[25,28,33] and a range of change between 6.6 and 18 μm[28,33,40,48]. This increase in CCT is associated with nocturnal corneal edema, caused by changes in osmolarity and hypoxia when closing the eyelids[50-51].

Read *et al*[36] concluded that there were significant differences in diurnal variations of CCT depending on the corneal region (central or peripheral at 1.75-3 mm from the center). Giráldez-Fernández *et al*[33] determined no difference in circadian changes in CCT between the central and peripheral cornea (1 to 2 mm) in healthy subjects. Glaucoma was also associated with a small but significant decrease in CCT throughout the day[37,39], peaking at 4:00[23-24]. The pattern of diurnal variation in healthy and glaucomatous eyes is similar, presenting no significant difference in the diurnal variation of CCT in any group[27]. Regarding eyes with Fuchs endothelial dystrophy, CCT only decreases during the first 4h after awakening, remaining stable thereafter[43]. Loreck *et al*[44] found a significant decrease in central and peripheral corneal thickness (1-2 mm from the center) between morning and afternoon.

In myopic orthokeratology users, CCT decreases between morning and night right after contact lens fitting at one night, one week, and three months[47]. This contact lens shapes the cornea overnight, inducing a heterogeneous change in corneal thickness, thinner at the center and thicker at the periphery[52]. During the waking hours, the cornea slowly recovers its original shape, meaning that diurnal variation in corneal thickness is inverse to the overnight effect: increasing at the center and decreasing at the periphery.

In eyes with pseudoexfoliation and eyes with keratoconus, there was a decrease in CCT throughout the day, with both groups presenting a maximum at 9:00 and a minimum at 17:00. The IOP followed this pattern as well[30,45]. Shen *et al*[35] determined that, in healthy subjects, there was a correlation between CCT and IOP all day, while the IOPcc only correlated with CCT at certain hours of the day (7:30, 13:00, 16:00, and 19:00). However, Hamilton *et al*[25] determined that IOP and CCT in healthy subjects correlated only between 7:00 and 9:00. Patients with glaucoma showed no correlation between diurnal variations in IOP and CCT[27,29]. Eyes with pseudoexfoliation presented a correlation between the diurnal fluctuations of both parameters[30].

Finally, Burfield *et al*[42] outlined that the diurnal variation of CCT was not different between emmetropic, hyperopic, or myopic subjects. However, Biswas *et al*[48] determined that emmetropic eyes presented a more significant change in IOPg and CCT than myopic eyes.

According to the literature revised, CCT can vary during the day and therefore its measurement should be also done at the same time point during the day if a correct pachymetric monitoring is intended to be done. The effect of circadian rhythms on CCT can also influence the measurement of IOP, and this aspect should be also considered.

Corneal Curvature The impact of circadian rhythms on corneal curvature presents mixed conclusions. Four studies stated that, in healthy eyes, the corneal radius decreases in the first hours after awakening, being stable afterward[25,33,39-40]. However, Villas-Bôas *et al*[39] and Hon *et al*[41] suggested that the corneal radius remained stable throughout the day. Only one study determined that corneal curvature flattened in the morning[48]. Lastly, Read and Collins[36] concluded that the anterior radius increased while the posterior radius decreased in the early morning after awakening. The anterior corneal meridian power correlated inversely to IOPg in healthy eyes[48].

In subjects with glaucoma, Villas-Bôas *et al*[39] suggested that corneal curvature did not present a significant variation throughout the day. In Fuchs dystrophy, the posterior corneal radius decreased during the first 4h after waking and remained stable[43]. Hamilton *et al*[25] determined that corneal curvature correlates with IOP and CCT between 7:00 and 9:00. However, Giráldez-Fernández *et al*[33] suggested a correlation between diurnal variations in corneal curvature and CCT.

According to the scientific literature revised, the clinical relevance of variations in corneal curvature during the day is not clear, with contradictory outcomes between authors. In any case, it is recommendable to take corneal shape measurements at the same time point in consecutive visits when performing a monitoring of corneal changes, as it is commonly done in keratoconus patients. In addition, these potential variations in corneal curvature should also considered in contact lens fitting. As lenses are worn throughout the day, the level of adequacy of fitting may be affected if diurnal changes of this morphological parameter are substantial.

Corneal Biomechanics Although non-contact tonometers, like the ORA, do not characterize biomechanical parameters directly related to the stiffness of the corneal tissue, some biomarkers, like CH and CRF, are under investigation for their plausible correlation to them[12]. These systems have limitations related to the nature of the loading stimulus. In particular, the air pulse induces a non-physiological tensional state in the corneal tissue (*i.e.*, bending stress) contrary to the physiological stress state (*i.e.*, membrane stress) induced by IOP. As such, non-contact biomarkers are influenced by the corneal tissue's biomechanical properties, corneal geometry (curvature and thickness), and intraocular pressure[53-54].

CH remains stable during the day for healthy young subjects[31-32,34-35,38]. Only Lau and Pye[40] showed an overnight increase of 0.4 mm Hg in CH. CRF presents a higher variation among studies. Lau and Pye[40], Chen *et al*[46], and Biswas *et al*[48] reported an increase in the first measurement of CRF taken after awakening, decreasing throughout the day. Although Oncel *et al*[38] and González-Méijome *et al*[34] reported a mostly stable CRF during the day, González-Méijome *et al*[34] remarked that there was a peak in the first measurement after waking, with a decreasing pattern and a posterior stabilization in the afternoon. In glaucoma patients, there was a consensus about CH and CRF remaining stable throughout the day[37,39]. However, only two studies in this narrative review used the ORA in glaucoma patients.

CRF correlates with CCT and IOP[13]. The diurnal fluctuations observed in CRF warrant exploration; it is essential to ascertain whether these shifts originate from inherent circadian rhythms or are consequentially linked to their associations with CCT and IOP, as both demonstrate circadian rhythmicity. Research indicated a correlation between CRF and diurnal variations of IOPcc, IOPg, and CCT[34-35,38]. Besides this, CH also correlates with CCT. In normal subjects, CH correlates inversely with IOPcc[35,38]. An intriguing demarcation emerges for glaucoma subjects; CH and IOP do not display a significant correlation within this population[37]. However, the direct factors influencing CH remain elusive, necessitating further studies.

Broadening the scope to corneal biomechanics, Kida *et al*[31] observed that while IOP changes are evident, there was no evidence to suggest that these variations induced shifts in the biomechanical properties of the cornea. Recently, Chen *et al*[46] introduced a new parameter related to corneal elasticity that correlated with IOP. The method to derive this parameter utilized the lamb wave model with a device combining a phase-resolved sweep source optical coherence tomography and a micro air-puff excitation technique[55]. This parameter remained consistent throughout the day in healthy individuals[46]. Hon *et al*[41] used an indentation system to demonstrate that corneal rigidity and tangential corneal modulus remained unchanged throughout the day.

According to the scientific literature revised, the level of variations of biomechanical properties of the cornea during the day remains unclear, with some authors detecting some significant changes, but others not. It should be also considered that some instruments used to monitor circadian rhythms have some limitations in really detecting the true modifications of the mechanical properties of the corneal tissue because their measurements are influenced by parameters such as CCT or IOP[53]. In any case, determining the impact of circadian rhythms on corneal biomechanics can be helpful to understand diurnal changes in some ocular parameters as well as to optimize and predict the results of some surgical procedures, especially in the context of keratoconus. More studies are needed to confirm if variations in corneal biomechanics can be related to some aspects, such as keratoconus progression, a poor orthokeratologic effect or contact lens complications.

CONCLUSIONS

Circadian rhythms significantly influence various corneal parameters, most notably IOP and CCT. There is a marked diurnal decline in IOP and CCT in healthy eyes and in eyes with Fuchs dystrophy. Additionally, the data revised about studies evaluating corneal morphological and biomechanical changes with circadian rhythms presents inconsistencies, especially concerning the diurnal variations in corneal curvature. Such disparities that may attributed to the different performance of the devices used underscore the importance of a consistent and standardized methodology in research. This variability holds immense clinical implications. For instance, the fluctuating IOP throughout the day is especially relevant for managing conditions like glaucoma, necessitating clinicians to be acutely aware of these oscillations when treating and monitoring patients. Unexplored areas remain, notably the biomechanical shifts induced by circadian rhythms in users of orthokeratology lenses. Their time-dependent efficacy makes it imperative to understand these diurnal variations to ensure optimal lens use. Furthermore, with keratoconus significantly impacting corneal biomechanics, there is an urgent need for comprehensive studies on eyes affected by this condition and those undergoing corneal collagen crosslinking.

It would be valuable to study the impact of some lifestyle habits, such as stress, diet, or sleep, on the diurnal variations of biomechanical and morphological parameters of the cornea. Moreover, some other factors to consider in this type of studies are the environmental conditions and measurement variability. Lastly, the small samples of the studies are linked to the limitation of the participant compliance, as the participants need to attend to the clinic several times per day for taking the clinical measurements required. While tools like the ORA system offer crucial insights, their day-long consistency in readings hints at the potential of alternative methodologies to uncover more subtle diurnal biomechanical changes. The existing research provides invaluable insights into diurnal variations of IOP and corneal parameters. However, research should emphasize larger sample sizes and uniform methodologies to ensure that findings are framed within their potential clinical implications, keeping the focus on patient-centered outcomes.

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