TITLE: A Review of the Link between Keratoconus and Posterior Segment Parameters:

SHORT TITLE: Keratoconus and Posterior Segment Parameters

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Abstract

Purpose: To review the published literature to understand the potential link between Keratoconus (KCN) and morphological and functional properties of the posterior segment structures.

Methods: The literature search included the Google Scholar, Scopus, ScienceDirect, and PubMed databases for the keywords “keratoconus, posterior segment, retinal structure, retinal function, retinal layers, choroid, optic nerve, optical coherence tomography, electrooculography, electroretinography, and visual evoked potentials”.

Results: Posterior segment changes are frequently found in patients with KCN, and several mechanisms have been proposed to explain this, including issues induced by oxidative stress in keratoconic corneas. In addition, other explanations could potentially stem from retinal adaptions to the distorted image that lands on the retina. Structural changes have been not only noted in several layers of the retina but also in the optic nerve head and the choroid.

Conclusion: It is clear from the extensive evidence in the literature that KCN can also be associated with morphological and functional changes in different structures of the posterior segment. When a KCN patient is diagnosed, it may be useful to consider assessing the retinal and choroidal profile using optical coherence tomography and potentially functional abnormalities through electrophysiology procedures. These evaluations aim to understand the best-case scenario vision gains that can be achieved and avoid surgeries, such as corneal transplantation, where patients are exposed to the risk of surgery and derive no additional visual benefit due to the presence of a posterior segment problem.

Keywords: Keratoconus, posterior segment, retina, choroid, optic nerve head.

1. Introduction

Keratoconus (KCN) is a bilateral, typically asymmetric corneal ectatic disease that manifests with thinning and protrusion but without clinical inflammation [1,2]. Even though the exact etiology remains uncertain, previous reports have hypothesized that genetic predispositions, ultraviolet light exposure causing oxidative damage, and mechanical factors (caused by eye rubbing in the setting of allergic diseases) are important factors in the pathogenesis of the KCN [3,4]. KCN generally induces progressive myopia and irregular astigmatism that causes increased higher-order aberrations and leads to reduced visual acuity, particularly corrected distance visual acuity (CDVA) [5,6]. However, the functional and structural changes of the anterior segment in KCN may affect not only the external ophthalmic tissues but also the internal ophthalmic structures of the eye [7].

Although prior studies have investigated the effects of KCN on structures of the anterior segment [8,9], little attention has been paid to the effects on the posterior segment. This lack of research often leads to the misconception that KCN is simply an anterior segment disease; however, KCN can be accompanied by posterior segment abnormalities. Possible interactions between the structural properties of the posterior and anterior segments of the eye have been hypothesized as there are continuous extensions of specific ocular structures that span from the anterior to the posterior segments [10]. Accordingly, it has been reported that posterior pole retinal thicknesses may change with KCN severity [11]. Previous case studies have reported the association and coexistence of KCN with degenerative retinal tissue changes in Ehlers–Danlos syndrome, retinitis pigmentosa, tapetoretinal degeneration, and Leber's congenital amaurosis [12-14]. Central serous chorioretinopathy and choroidal neovascularization have also been observed concurrent with KCN [15,16]. However, there are very few published studies as case reports about the concurrent presentation of KCN and retinal diseases and the common pathological properties of these ocular diseases are not entirely obvious. Fundamentally, the

evaluation of retinal health in patients with KCN could be an essential part of their clinical course, which is especially important to know when corneal graft surgery is being considered [15,17]. This review aims to provide a comprehensive review of the microstructural and functional changes of the non-pathological retina in the eyes of patients with KCN.

2. Methods

2.1. Literature search

The keywords of this literature review article were extensively searched on Google Scholar, Scopus, ScienceDirect, and PubMed search engines for original scientific articles. A total of 136 articles published from January 1, 1988, through May 1, 2021, for randomized clinical trials (RCTs), meta-analyses, systematic reviews, and observational studies included the following keywords in various combinations were retrieved: keratoconus, KCN, cornea, posterior segment, retina, retinal structure, retinal function, retinal layers, retinal nerve fiber layer, RNFL, retinal pigment epithelium, RPE, choroid, optic nerve, optic nerve head, optical coherence tomography, OCT, enhanced-depth imaging, electrooculography, electroretinography, and visual evoked potentials. A thorough review of all publications in English and the abstracts of non-English papers was undertaken. The reference lists of the selected works were also checked for potentially relevant articles. Selected sources were also mutually agreed upon by the authors. Irrelevant articles to the primary aims of the study were excluded.

3. Posterior segment evaluation

Optical coherence tomography (OCT) is a well-established non-contact and non-invasive optical imaging modality and has micron resolution allowing quantitative and qualitative assessment of the various ocular structures *in vivo*. It has been shown that OCT measurements are reliable and repeatable for assessing both anterior and posterior segment structures [18,19]. OCT is routinely used in the diagnosis and monitoring of retinal diseases such as age-related macular

degeneration, diabetic retinopathy, uveitis, and central retinal vein occlusion [20], and the choroid can be imaged using a modality called enhanced depth imaging (EDI)-OCT [21].

Previous reports indicated that certain parameters such as age, race, refractive error, and axial length could affect OCT findings in the retina [22]. Although corneal irregularities present in KCN can compromise the optical quality of OCT retinal images, the technique can still reliably record retinal layer thicknesses in these patients [7,23-26].

Other posterior segment imaging modalities such as fluorescein angiography (FA) and B-scan are not applicable in assessing morphological changes of the retinal and choroidal profile. It is due to their inability to acquire cross-sectional images of the posterior segment (in case of FA) or low-resolution imaging system (in case of B-scan).

4. Connections between keratoconus and retinal structures

4.1. Keratoconus and central retinal thickness

KCN can be accompanied by microscopic defects in the macular area that are not observable during routine ophthalmoscopic evaluations, meaning that the poor visual acuity of patients with KCN might not be attributed simply to the corneal disorder, but also retinal abnormalities [7].

Deonarain et al., in a cross-sectional study, compared the central foveal thickness (CFT) values of non-KCN subjects (control group) with three groups of patients with KCN at different stages of the disease (study groups, according to the Collaborative Longitudinal Evaluation of KCN [CLEK] study classification system) [27]. They found no significant differences in CFT measurements between the control and three study groups. Previous studies comparing KCN patients with matched non-KCN subjects revealed similar findings in CFT measurements [7,11,17,28]. Fard et al., in a cross-sectional cohort study, noted a direct correlation between KCN severity (According to the ABCD grading system) and the average value of whole retinal thickness measurements (R^2 = 0.422); however, they also found similar values of CFT between

KCN and non-KCN patients [11]. Uzunel et al., in a cross-sectional study, found no significant differences in CFT between non-KCN and KCN patients with grades 1 and 2 (according to the Amsler-Krumeich classification system), whereas patients with grade 3 had significantly lower CFT values than non-KCN subjects [29]. According to the data analyses, they reported that severe cases of KCN would be associated with thinner CFT values. They did not propose any underlying theory for this finding. Brautaset et al. and Moschos et al. (using Stratus OCT device, compared CFT values between KCN and non-KCN participants, and found non-significant differences of 4 μm and 7 μm, respectively [17,7]. In a comparative cross-sectional study on pediatric KCN patients and non-KCN age-matched subjects, Yilmaz et al. observed a similar trend [28]. However, they reported a non-significant difference value of 18 μm between the study and control groups.

On the other hand, Sahebjada et al., in a cross-sectional study, reported significantly higher mean CFT values (10 μm thicker) in patients with KCN than in non-KCN subjects [26]. The authors concluded that CFT might not be influenced during the initial stages of KCN, and the changes are mainly manifested when progressing to the more advanced severities. They hypothesized that the higher CFT values of KCN than non-KCN subjects might be attributed to the compensatory retinomotor movements of photoreceptors following form deprivation. This theory had been suggested in previous animal studies in which imposed unilateral form deprivation could produce morphological changes in the retinal structure of the affected eye compared to the unintervened fellow eye [30,31]. Likewise, several human studies on anisometropic amblyopia revealed increased CFT values in the form of deprived amblyopic eyes compared to non-amblyopic eyes [32,33]. According to these findings, it could be theorized that the CFT of advanced KCN eyes could be thickened secondary to the retinomotor movements of photoreceptors, in order to offset the vision degradation induced in such patients. Another explanation for higher CFT in individuals with advanced KCN has been attributed to the

compensatory growth of the retinal tissue in response to the structural disorders of the corneal thinning to prevent overall ocular disorganization [26]. The results of Lei et al. support this theory, as they observed postsurgical increase of macular volume as revealed by OCT in patients who underwent a laser in situ keratomileusis (LASIK) procedure [34]. Accordingly, changes in optical parts of the eye may be compensated by changes in posterior segment morphology; however, this is still a relativity unproven theory and requires further investigations. In addition, a limitation of most previous studies on retinal changes in KCN participants was that they were cross-sectional in nature. Therefore, future longitudinal studies should be performed to better analyze the changes of the posterior segment during KCN progression over time.

Despite the success of the work by Sahebjada et al. in certain aspects, it still suffers from statistical issues [26]. The reported significant value of 10 μm might be attributed to the larger sample size of participants (87 KCN and 67 non-KCN subjects) compared to other studies, although the study participants were not matched by age (mean ages: 35 years and 44 years for the KCN and non-KCN groups, respectively). Gender differences were also significant (61.5% males vs. 38.5% females). According to the findings of the previous studies, retinal thickness values were lower in females than in males and tended to decrease with aging [35,36]. In other words, failure to control for the effects of demographic characteristics between eyes with and without KCN when assessing CFT can compromise the validity of the comparisons. However, another possible explanation for the contradictory results reported to date may be the different OCT devices and different segmentation algorithms of the outer and inner retinal borders used in these studies [27].

Table 1 summarizes studies comparing CFT findings in KCN patients.

4.2. Keratoconus and paracentral retinal morphology

KCN may be associated with changes in various locations across the retinal tissue. Deonarain et al. found no significant differences in mean thickness measurements of different parafoveal and perifoveal quadrants across the retina between non-KCN and mild, moderate, and severe KCN patients [27]. Brautaset et al. also found no significant differences between KCN and non-KCN individuals in terms of mean retinal thickness values at different parafoveal locations of the retina [17]. On the other hand, Sahebjada et al. in their study reported significantly higher values of retinal thickness at parafoveal and perifoveal locations for the KCN study group than the non-KCN control group [26]. However, as mentioned previously, despite statistically significant findings of their study, the reported values of thickness differences were close to those findings of the previous studies [17,26]. In addition, they did not analyze thickness measurements of retinal layers separately to determine which layer(s) might increase in thickness in patients with KCN. In children aged between 8 to 14 years old, Yilmaz et al. reported no significant difference in central and parafoveal retinal thicknesses between children with and without KCN [28]. In a cross-sectional cohort study, Fard et al. investigated the thickness pattern across the retinal tissue in KCN patients with different disease severities [15]. They found significantly higher average thickness values of superior and inferior hemifields in KCN patients compared to non-KCN patients.

4.3. Further parameters affecting retinal morphology in keratoconus patients

The presence of higher and more fluctuating amounts of corneal astigmatism in those with KCN than in those without KCN might be another effective factor of CFT changes in keratoconic eyes [5,37]. Uzunel et al. in a cross-sectional comparative study found no significant differences in the retinal thicknesses of KCN patients before and after correction of astigmatism by gas permeable lenses [38]. Hwang et al. conducted a study where astigmatism refractive error was induced by wearing toric soft contact lenses [39]. They found no significant differences in CFT when comparing astigmatism-induced eyes with corresponding baseline data of the same eyes

[39]. In another study, patients with KCN who underwent collagen cross-linking (CXL), Romano et al. observed that patients displayed no significant change in retinal thickness or CFT at baseline and six months after the CXL procedure, despite significant differences in mean corneal astigmatism values between the four study groups [40].

Axial length (AL) differences might be related to the retinal thickness measurements [41-44]. However, there are conflicting results regarding the effect of AL on OCT measurements in non-KCN myopic subjects [41-44]. Uzunel et al. performed a study assessing AL and CFT values in KCN patients (as a sub-test) and found no significant difference in mean AL measurements with changes in average CFT values (mean values of AL were 23.06, 23.41, 23.27, and 23.13 for control, KCN grade 1, grade 2, and grade 3, respectively) [29]. Sahebjada et al. found that despite a higher CFT value in KCN than non-KCN participants, there was no significant difference between AL measurements of KCN and non-KCN subjects (mean values of 24.1 for KCN and 23.8 for non-KCN subjects) [26].

Scan quality index (SQI) or signal strength is another possible explanation for retinal changes observed in people with KCN. Although a lower scan quality index (SQI) or signal strength is suggested as a possible explanation for retinal changes observed in people with KCN [17,27,29], SQI may not affect OCT segmentation and the reliability of OCT measurements [45]. In addition, in Deonarian et al.'s study, the lower SQI in KCN participants was still higher than the recommended cut-off value for reliable OCT measurement, thus not undermining the OCT interpretations [27,40].

4.4. Proposed etiologies of gross retinal changes in keratoconus

The pathophysiological mechanism of gross retinal thickness changes in KCN remains unknown, although several theories have been proposed. The first theory explains the compensatory response of the posterior segment according to the Stiles–Crawford effect (SCE)

of the first kind [46]. According to this phenomenon, when the oblique light rays entering the eye, which pass through the pupillary margins, a remarkable decline in luminous efficiency occurs. In this situation, the directional sensitivity of the photoreceptors diminishes and retinal tissue adapts to offset against decreased light intensity by intensifying the absorbance of the central incident light rays that are brighter. Due to the compromised retinal image and excessive HOAs, patients with KCN theoretically have a multifocal-structured cornea [47]. This causes a reduction in the incidence light intensity, which is similar to the time when dimmer oblique light beams enter the eye from the pupil margins (as proposed for the SCE phenomenon). This occurrence thereby may evoke the SCE of the first kind. However, the effect of this phenomenon on retinal morphology is not well understood. The second explanation for gross retinal changes associated with KCN could be assigned to another compensatory mechanism known as photostasis. This process is a prolonged adaptive reaction of retinal photoreceptors, developed in response to the changes in environmental lighting conditions [48,49]. Photostasis mainly occurs in rods to keep the retinal capacity of photon absorption at a constant level and subsequently retain the saturation of rod cells under photopic conditions [50]. Photostasis predominantly causes the outer part of rod cells to be elongated [49,50]. Impaired optical properties of the cornea in KCN patients result in diminished incident light intensity reaching the photoreceptors. This condition imposes functional disorders to the eye and is similar to long-term light deprivation. Therefore, the photostasis of the photoreceptors acts as a compensatory response [51].

5. *Keratoconus and different layers of the sensory retina*

OCT recording is a reliable and repeatable tool for RNFL thickness measurements of KCN [52], as well as non-KCN subjects [53]. Several studies have investigated changes in different layers of the sensory retina. The majority of these studies focused on retinal nerve fiber layer (RNFL), and retinal ganglion cell layer (RGCL) changes in KCN patients. Cuppusamy et al., in a

comparative study, investigated the measurements of RNFL and RGCL thickness in KCN patients [54]. They found comparable results of these two parameters between KCN and non-KCN participants. The Control group, which included non-KCN subjects, showed non-significantly thicker values of overall RNFL thickness of either eye compared to KCN patients, similar to findings from previous studies [55]. In another comparative study, Uzunel et al. analyzed the effect of different stages of KCN on RNFL and RGCL measured by OCT [29]. They observed a negative correlation between thickness values of peripapillary RNFL and RGCL with higher stages of KCN compared to non-KCN subjects. Despite their valuable results, they did not evaluate the differences in thickness values in macular areas. On the other hand, Bayhan et al. in a prospective study found a significantly thinner RGCL and a non-significant difference, but thinner RNFL measurement in people with KCN than in the non-KCN group [56]. Cankaya et al. in a cross-sectional and observational study analyzed RNFL thickness measurements of 46 patients with KCN and 74 age- and gender-matched non-KCN study participants [23]. Similarly, they also found a non-significantly thinner RNFL in KCN participants compared to non-KCN individuals. They attributed these changes to the increasing trend of irregular astigmatism and subsequent degradation of retinal image quality in patients with progressive KCN. The authors also noted that the magnitude of RNFL thickness was more comparable than optic nerve head parameters when comparing KCN and non-KCN patients. However, it is notable that they did not categorize KCN individuals according to the KCN severity.

Clinically, the induced astigmatism error in KCN patients may act as an artifact while imaging acquisition by OCT. Langenbucher et al. demonstrated that high degrees of astigmatism in more advanced cases of KCN might bring changes in peripapillary RNFL findings [57]. They assigned these changes to the elliptical distortion and subsequent size variations of the projected image on the retina. Likewise, Hwang et al. noted that astigmatism error might exert

different effects on RNFL measurements at different peripapillary locations [39]. They found a reduction of RNFL thickness measurements in the superior and inferior retinal zones and nasal and temporal retinal zones following imposed with-the-rule and against-the-rule astigmatism, respectively. Leonard et al. analyzed the quantity and quality of the projected retinal image of KCN subjects by using objective scatter index (OSI) and point spread function (PSF), respectively [58]. They found that despite the higher OSI values in most KCN patients, retinal image quality was more profoundly decreased in advanced cases of KCN. The authors assumed that the decline in retinal image quality might be due to the remarkable ellipsoid pattern of the projected images in severe cases of KCN. They concluded that OSI as an objective parameter could aid clinicians in early KCN detection as well as the staging process of patients with KCN.

Few studies have investigated all layers of the sensory retina separately. Özsaygılı et al. in an observational clinical study compared the thickness changes of sensory retinal layers in all stages of KCN except stage-4 (according to the Amsler-Krumeich staging system) with age, sex, and axial length-matched non-KCN study participants [59]. They analyzed thickness measurements of RNFL, RGCL, inner plexiform layer (IPL), inner nuclear layer (INL), outer plexiform layer (OPL), and outer nuclear layer (ONL) with an automatic segmentation program of a spectral-domain OCT device across the central retinal areas. There were no statistically significant differences between all stages of KCN and non-KCN subjects in all sensory retinal layers except INL. The INL was significantly thinner in non-KCN subjects compared to KCN patients with stages 2 and 3. In comparing INL thickness values between KCN subjects, those patients with more advanced KCN had significantly thicker INL than less severe cases. The authors claimed that the higher INL thickness in more severe cases of KCN could be due to activation of Müller cells in response to the augmented oxidative stress of KCN corneas. They

concluded that KCN is associated with INL thickening, where the bodies of neuroglial cells are situated.

Several theories have been proposed to explain the changes in the morphology of sensory retinal layers in KCN subjects. It has been demonstrated that the corneal tissue of people with KCN contains higher quantities of nitrotyrosine than non-KCN people. The presence of this product is a marker of cell injuries and inflammations as well as nitric oxide (NO) synthesis at sites of stromal tissue breakdowns [60]. Raised reactive oxygen species (ROS) formation in KCN eyes results in oxidative stress and subsequent disruption of mitochondrial DNA (mtDNA) [3]. This phenomenon causes a malfunction in locations of protein-encoding mtDNA followed by degradation of mitochondrial oxidative phosphorylation and further oxidative injury. Diminished antioxidant reactions of corneal tissue in KCN patients could also trigger keratocyte apoptosis. Increasing keratocyte apoptosis and oxidative stress in the anterior segment of KCN patients may also affect the crystalline lens and the posterior segment tissues [61].

Previous studies advocated other theories besides oxidative stress to explain the relationship between retinal morphology changes and KCN progression. Clinically, KCN is considered a multifactorial disease, and various environmental and genetic factors play a role in the pathogenesis of the disease. Previous findings of genotyping studies performed on KCN and control subjects demonstrated a potential association between genes involved in age-related macular degeneration (ARMD) and KCN [62]. Cao et al. found that single nucleotide polymorphisms (SNPs) located on rs6795735 in the ADAMTS9 gene and rs5749482 in the TIMP3 were presented in both ARMD and KCN [62]. Lee et al. also reported a significantly lower expression rate of these two genes in KCN patients than non-KCN individuals [63].

6. *Keratoconus and retinal pigment epithelium layer*

Few studies have investigated the retinal pigment epithelium (RPE) layer changes accompanied by KCN. Özsaygılı et al. by comparing KCN patients with different severities and non-KCN subjects found a significantly decreasing trend in RPE layer thickness along with increasing KCN severity [59]. They proposed that elevated ROS levels and reduced antioxidant activities of the tissue in keratoconic eyes could result in cellular injuries at the photoreceptor level and the RPE layer due to cellular apoptosis [64]. Histologically, the number and thickness of these components are likely to be decreased when affected by oxidative stress [65]. They also hypothesized that some genetic factors might be a source of RPE thinning in their participants, especially in advanced cases of KCN. However, further studies are recommended to clarify the proposed relationships.

7. *Keratoconus and optic nerve head parameters*

The effect of KCN on optic nerve properties was infrequently investigated in contrast to other structures of the posterior pole. Several studies evaluated the effects of corneal properties on the optic nerve head (ONH) parameters in glaucomatous and non-glaucomatous patients [66-69]. Cankaya et al., in a cross-sectional study on a healthy population, found that corneal thickness was inversely associated with disc area [68]. Other studies advocated this finding [69]. In another study, Cankaya et al. analyzed ONH characteristics of non-glaucomatous KCN subjects using confocal scanning laser ophthalmoscopy [23]. They reported significantly larger disc and cup areas, thinner RNFL measurement, and deeper cup depth in KCN patients than non-KCN individuals. Their findings were consistent with previous studies that reported the same results on thin corneas [10,66,69]. They speculated that these associations might be attributed to the continuous collagen tissue extension of the cornea and sclera. Postolache in a study compared the optic nerve head parameters of children with Down syndrome to healthy subjects [70]. They found smaller and relatively tilted optic disc in Down syndrome. As KCN is commonly observed in patients with Down syndrome and may be associated with severe degrees of myopia and

oblique astigmatism, they assumed that optic disc hypoplasia and tilting and visual acuity reduction in Down syndrome might be attributed to the presence of KCN [71,72]. However, they noted that reduced vision in children with Down syndrome could not specifically assign to the abnormalities of the optic disc or KCN. Clinically, patients with Down syndrome encounter various ophthalmic and neurosensory disorders. Ciftci reported a case of unilateral tilted disc syndrome that coexisted with KCN in the same eye [73]. Therefore, it is noteworthy that ONH and RNFL evaluation of KCN patients suspected of glaucoma should be performed cautiously.

8. *Keratoconus and choroidal structure*

KCN may be associated with morphological changes in choroidal structure [74-76]. Gutierrez-Bonet et al. in a prospective, cross-sectional study using EDI imaging of swept-source OCT, observed a higher subfoveal choroidal thickness (ChT) in KCN patients compared to non-KCN subjects [74]. This finding agreed with the results of Akkaya, and Pinheiro-Costa et al [75,76]. However, the underlying mechanism of choroidal thickening in KCN patients remains uncertain, but the associated inflammatory events of the choroid might be considered as a possible precipitating factor [75]. Bilgin and Karadag found the same results and claimed that ChT could be considered a novel clinical indicator of disease progression in KCN patients [77]. However, Pinheiro-Costa et al. opposed this theory and claimed that ChT evaluation is not a helpful marker of disease progression in KCN patients [78].

According to the literature review, the effects of KCN on various structures and functions of the posterior segment of the eye and the proposed underlying mechanisms are interesting and essential subjects for future studies.

9. Links between keratoconus and retinal function

Electrophysiology can be used to assess the functional integrity of the retinal layers (i.e., its ability to transduce light into neural impulses) and post-retinal neural pathway, and is an

essential technique in helping diagnose the causes of unexplained vision loss [79]. The three most common testing protocols of electrophysiological examinations are electroretinography (ERG), electrooculography (EOG), and visual evoked potential (VEP) assessments [80]. **Table 2** summarizes the specifications of electrophysiology testing methods and their corresponding anatomical sources as well as their clinical indications.

Multiple studies have shown that anterior segment disorders, including irregular corneal astigmatism, refractive errors, and corneal opacities, can impact upon ERG recordings [81-83]. Several studies have also reported an association between KCN and electrophysiological abnormalities [84,85]. Moschos et al. observed significant decreases in retinal response density (RRD) of multifocal-ERG (mfERG) recordings in patients with KCN compared with matched non-KCN subjects, with decreased RRD being associated with lower BCVA [7]. Macular dysfunction associated with KCN is therefore likely to aggravate reduced visual acuity. Their finding reinforced the possibility of concurrent photoreceptor dysfunction in KCN patients. They concluded that poor visual acuity of KCN patients might not only be caused by corneal disorders but also by posterior segment dysfunction. In addition, the authors suggested that electrophysiological evaluation of KCN patients before corneal transplant surgeries may provide helpful information in predicting postsurgical visual improvement. In order to test this concept, Moschos et al. analyzed ERG and VEP recordings of 233 patients with KCN to determine the frequency of retinal pathologies within that population [13]. They observed six cases where ERGs were extinguished, and VERs were pathologic. There were four cases where ERGs were normal, and VERs were pathologic, suggesting that KCN can coexist with diffuse tapetoretinal degenerations or macular lesions, noting that preoperative application of mfERG could prevent unnecessary corneal transplant surgeries. One such example already exists in the literature; Fogla et al. reported the a patient whose visual acuity of the left eye failed to improve after an uneventful bilateral corneal graft surgery [85]. Postsurgical ERG assessment revealed

manifestations of cone-rod dystrophy. Nguyen et al.(84) also reported a 35-year-old patient with KCN with retinal congenital stationary night blindness (CSNB) type 1, who showed no response to a dim flash in the scotopic in response to attenuated tests under photopic conditions. The ERG recording also showed a “negative” response with a near plateau response of b-wave.

Despite the available studies in the field of KCN and its ERG and VEP presentations, no published study investigated the effects of KCN on EOG measurements. However, as EOG reflects the functional integrity of RPE layer and due to the previous finding of RPE involvement in KCN [59]. it is probabple EOG measurements be affected by the presence of KCN.

Consequently, electrophysiological evaluations are essential in KCN patients with unexplained reduced vision who do not manifest visible retinal disorders. The preoperative evaluation of retinal function is particularly crucial in those patients who are candidates for corneal transplant surgery.

10. Conclusions

There is always the possibility that when a patient presents with both KCN and a retinal pathology, the presence of both is a coincidence and that their etiologies are independent. However, on review of the literature, this may be the exception rather than the rule in these cases of co-morbidity. It appears that KCN can alter retinal, choroid, optic nerve head morphology, as well as retinal function. There are several proposed mechanisms regarding the microstructural changes of a weakened cornea, including chemical factors related to increased oxidative stress of the keratoconic corneas and retinal adaptation to the disturbed optical input that the retina receives from KCN corneas, which are highly myopic and irregularly astigmatic.

There is a strong rationale for screening the retinae of patients with KCN (by OCT and even electrophysiology, whenever possible), in part to determine whether patients’ vision losses are entirely due to the disease process in the cornea, and also in part to make better-informed

choices regarding performing interventions, such as corneal transplants, that will expose patients to the risks of surgery, but do not deliver any additional visual benefit, because retinal issues exist.

Conflict of interest statement: The authors did not receive any financial support from any public or private sources.

Disclosure: The authors have no financial or proprietary interest in a product, method, or material described herein

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Table 1. Summary of studies on central foveal thickness measurements using optical coherence tomography in keratoconus patients

Study (First Author/Year)	Study type	Number of eyes	Mean age (in years)	OCT device	KCN classification system	Main finding(s) (in terms of mean CFT)	Additional central OCT finding(s)
Moschos et al. (2013) [7]	Comparative, Cross-sectional	64 (KCN) 60 (non-KCN)	33.9 (KCN) 34.4 (non-KCN)	TD-OCT (Stratus OCT3; Carl Zeiss Meditec)	NC	No significant difference between KCN and non-KCN (p=0.317)	No additional data
Brautaset et al. (2015) [17]	Comparative, Cross-sectional	44 (KCN) 80 (non-KCN)	37.3 (KCN) 37.6 (non-KCN)	SD-OCT (Cirrus HD OCT; Carl Zeiss Meditec)	CLEK	No significant difference between KCN and non-KCN (p=0.491)	No significant differences in cube volume (p=0.343) and cube average thickness (p=0.466) between KCN and non-KCN subjects
Sahebjada et al. (2015) [26]	Comparative, Cross-sectional	129 (KCN) 174 (non-KCN)	35 (KCN) 44.25 (non-KCN	TD-OCT (Stratus OCT3; Carl Zeiss Meditec)	NC	Significantly higher values in KCN than non-KCN (p < 0.05)	Significantly higher IMT, OMT, IMV, and OMV values in KCN than non-KCN (p < 0.005) No significant difference in CFT value between early KCN (patients with no evidence of corneal scarring/haze/opacities, average keratometry ≤ 47.0 D) and non-KCN (p=0.2)
Uzunel et al. (2017) [29]	Comparative, Cross-sectional	84 (KCN): Grade1=29 Grade2=29 Grade3=26 29 (non-KCN)	29.7 (Grade1) 31.6 (Grade2) 33.8 (Grade3) 29.1 (non-KCN)	SD-OCT (Cirrus HD OCT; Carl Zeiss Meditec)	A-K	No significant difference between KCN grade1, grade 2 and non-KCN Significantly lower values in KCN grade3 than non-KCN (p < 0.001)	Significantly lower central subfield thickness, cube volume, and average cube thickness values in KCN than non-KCN (p < 0.001)
Yilmaz et al. (2018) [28]	Comparative, Cross-sectional	50 (KCN) 50 (non-KCN)	12.4 (KCN) 12 (non-KCN	SD-OCT (Spectralis; Heidelberg Engineering)	NC	No significant difference between KCN and non-KCN (p=0.89)	Pearson correlation analysis revealed no significant correlation between CFT value and corneal topography parameters (average SimK [r= 0.281, p= 0.51], corneal volume [r= 0.014, p= 0.93], and corneal apex power[r= 0.135, p= 0.36])
Deonarain et al. (2019) [27]	Comparative, Cross-sectional	44 (KCN): Mild=15 Moderate=11 Severe=18 44 (non-KCN)	25.53 (Mild) 25.45 (Moderate) 23.33 (Severe) 24.61 (non-KCN)	SD-OCT (iVue-100; Optovue)	CLEK	No significant significant difference among the non-KCN and three KCN groups (p= 0.199)	No additional data

Fard et al. (2020) [11]	Cohort, Cross-sectional	48 (KCN) 28 (non-KCN)	30.9 (KCN) 36.3 (non-KCN	SD-OCT (Spectralis; Heidelberg Engineering)	Belin ABCD	No significant difference between KCN and non-KCN (p=0.13)	The correlation between KCN severity for the central retinal zone was $R^2 = 0.296$, $p = 0.01$

Abbreviations: ***OCT:*** Optical coherence tomography; ***KCN:*** Keratoconus; ***CFT:*** Central foveal thickness; ***TD-OCT:*** Time-domain optical coherence tomography; ***SD-OCT:*** Spectral-domain optical coherence tomography; ***NC:*** Not classified; ***CLEK:*** Collaborative Longitudinal Evaluation of Keratoconus study; ***A-K:*** Amsler–Krumeich Classification; ***IMT:*** inner macular thickness; ***OMT:*** outer macular thickness; ***IMV:*** inner macular volume; ***OMV:*** outer macular volume;

Supplemental Table1. Summary of specifications and clinical indications of three electrophysiology examinations; electroretinography (ERG), electrooculography (EOG), and visual evoked potential (VEP)

Test	Sub-tests	Stimulus configuration	Retinal adaptation	Wave origin	Clinical indications
ERG	*Flash ERG*	Flashing light	LA and DA	- Photoreceptors (a-wave) - Bipolar and Müller cells (b-wave) - RPE cells (c-wave)	- Degenerations and dystrophies of the retina and the choroid - Regular monitoring of the posterior segment acquired diseases
	Pattern ERG	Equally sized black and white checkerboards	LA	- Macular photoreceptors (P50) - Ganglion cells (N95)	- Assesing macular and optic nerve dysfunctions
	mfERG	Different sized lack and white hexagonals	LA	- Centrally located cone cells	- Regular monitoring and evaluation of localized retinal toxicity in the macular area
EOG	---	Two laterally-placed fixation lights in a full field dome-shaped stimulator	LA and DA	- RPE cells	- Evaluation of posterior segment diseases affecting RPE layer
VEP	*Pattern VEP*	Equally sized black and white checkerboards	LA	- Optic nerve to cortx neural pathway	- Assessing optic nerve integrity - Assessing potential visual acuity in young and nonverbal children
	mfVEP	Black and white dartboard pattern	LA	- Striated cortex	- Local and multiple dysfunction in the visual field, especially ganglion cells defects

ERG: electroretinography; ***mfERG:*** multifocal-ERG; ***VEP:*** visual evoked potential; ***mfVEP:*** multifocal-VEP; ***EOG:*** electrooculography (EOG); ***LA:*** light adapted; ***DA:*** dark adapted; ***RPE:*** retinal pigment epithelium