



## Case report

## Keratoconus progression associated with hormone replacement therapy

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## ABSTRACT

**Purpose:** To report a postmenopausal patient with keratoconus who experienced significant progression after using hormone replacement therapy.**Observations:** A 51-year-old woman with previously stable keratoconus presented with acute disease progression following hormone replacement therapy in the context of prophylactic hysterectomy and bilateral ovariosalpingectomy. Over a 14-month period after starting hormone therapy, the steepest K increased from 63.7D to 71.5D in the right eye and from 65.8D to 78.1D in the left eye.**Conclusions:** Hormone replacement therapy may amplify progression of keratoconus.

## 1. Introduction

Keratoconus is a progressive, non-inflammatory corneal ectasia that can lead to severe impairment of vision.<sup>1</sup> Keratoconus is one of the most common indications for keratoplasty in the United States.<sup>2</sup> Individuals with this condition most commonly present during adolescence, after which there is a period of progression for approximately 10–20 years.<sup>1</sup> The etiology of the disease has not been fully delineated.<sup>1</sup> In recent years, there has been considerable interest in the influence of hormones on keratoconus progression.<sup>3–5</sup> Previous reports have implicated estrogens, progesterone, and thyroid hormones in the alteration of corneal biomechanics.<sup>5–7</sup> Case reports detailing keratoconus progression following pregnancy<sup>3,8</sup> and *in vitro* fertilization (IVF)<sup>9</sup> have been published. To further support the effects of sex hormones on this condition, herein we report a case of keratoconus progression in a postmenopausal patient treated with hormone replacement therapy (HRT).

## 2. Case report

A 51-year-old woman with a history of keratoconus presented to our facility with a subacute reduction of visual acuity in both eyes.

Prior to age 28 the patient reported having uncorrected vision of 20/20 in both eyes. At the age of 29, the patient received hormone therapy related to IVF and was diagnosed with keratoconus shortly after the birth of her child. Although we were unable to obtain medical records prior to her pregnancy, we reviewed the medical records following her initial diagnosis. For the next 20 years, the patient was managed with rigid gas permeable (RGP) contact lenses. Her annual

keratometry and topography during the next 17 years exhibited minimal disease progression (Fig. 1).

Two years prior to presentation at our clinic, the patient underwent a prophylactic hysterectomy and ovariosalpingectomy in the context of BRCA gene mutation. HRT with estrogens and progesterone was commenced postoperatively. After experiencing fluctuations in vision for two years she attended our facility for ophthalmic evaluation. Associated symptoms included ocular itching and intermittent burning sensation, yet despite these symptoms the patient denied rubbing her eyes. The patient's previously well-tolerated RGP contact lenses were causing her significant discomfort, and the patient noted recent onset of copious mucus discharge.

On examination, the best spectacle corrected visual acuity was 20/50 in the right eye and 20/100 in the left eye. With RGP contact lenses, the vision improved to 20/40 in both eyes. Slit lamp examination revealed conjunctival follicles, keratoconus, and inferior punctate epithelial erosions in both eyes, as well as a Fleischer ring and apical opacity in the left eye. Anterior segment tomography with Pentacam demonstrated inferior steepening in both eyes, with progression relative to her previous exams (Table 1).

Due to concerns about further progression, a close follow-up was scheduled. Furthermore, the patient was prescribed hybrid contact lenses rather than RGP lenses. The patient was highly satisfied with her hybrid contact lenses at the six-month follow-up, and best-corrected visual acuity with spectacles at this time was 20/30 in the right eye and 20/50 in the left eye. Nevertheless, corneal tomography demonstrated further progression (Table 1). Clinic notes from this encounter acknowledged that these alterations in corneal tomography might have

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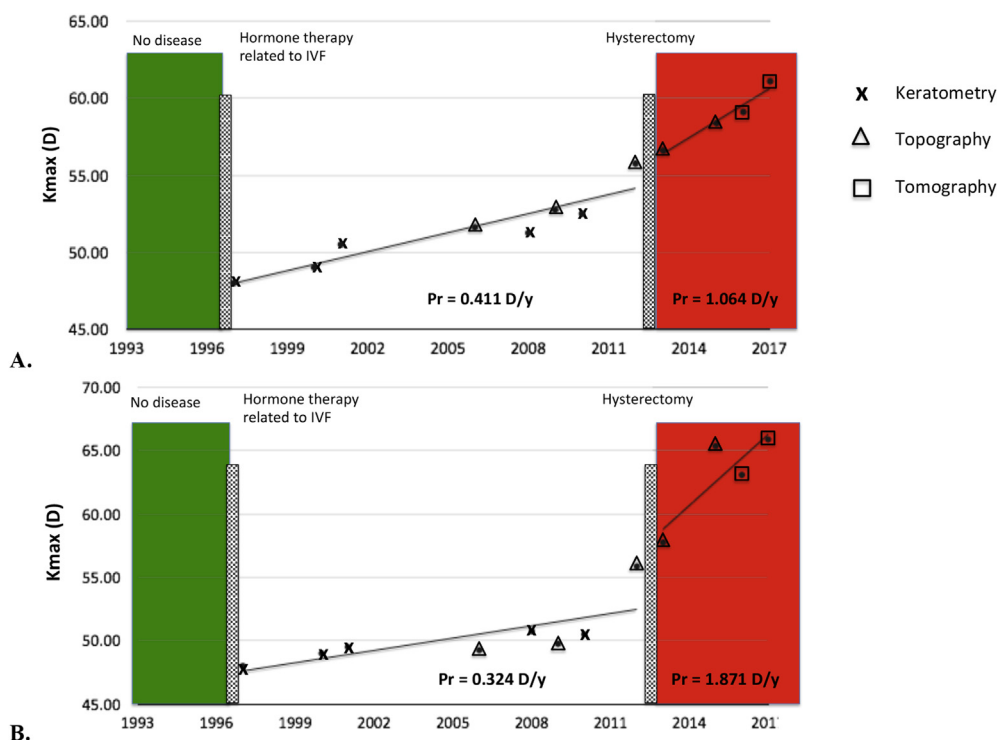


Fig. 1. Keratoconus progression over the course of 20 years in the right eye (A) and in the left eye (B) with its association with *in vitro* fertilization (IVF) treatment and hysterectomy. Pr = progression rate.

**Table 1**  
Tomography (Pentacam) of both eyes.

Tomography (Pentacam) Right Eye									
OD	VA cc	VA contacts	Steep K	Anterior Elevation	Posterior Elevation	Thinnest point	Kmax	Km front	Km back
Baseline	20/50	20/40	63.7D	+ 30µm	+ 81µm	432µm	56.4D	56.2D	- 8.3D
6 months	20/30 + 2		69.2D	+ 49µm	+ 101µm	447µm	59.1D	58.2D	- 8.8D
10 months	20/30	20/30	67.2D	+ 41µm	+ 79µm	457µm	59.7D	58.8D	- 8.7D
14 months	20/40	20/30	71.5D	+ 48µm	+ 89µm	490µm	60.7D	59.7D	- 8.8D
Tomography (Pentacam) Left Eye									
OS	VA cc	VA contacts	Steep K	Anterior elevation	Posterior Elevation	Thinnest point	Kmax	Km front	Km back
Baseline	20/100	20/40	65.8D	+ 69µm	+ 137µm	401µm	59.9D	55.0D	- 6.6D
6 months	20/50		74.5D	+ 78µm	+ 158µm	427µm	63.1D	60.1D	- 8.0D
10 months	20/40	20/25-1	79.0D	+ 88µm	+ 172µm	369µm	62.1D	61.3D	- 7.9D
14 months	20/300	20/20-1	78.1D	+ 81µm	+ 143µm	410µm	65.5D	60.7D	- 8.8D

VA cc = BCVA with spectacles; VA contacts = BCVA with contact lenses; µm = micron.

resulted from the recent change to the patient's contact lenses; nevertheless, regular follow-up was continued given the concerns regarding keratoconus progression. These concerns were realized when further progression was noted at two subsequent follow-up exams (Table 1 and Fig. 2).

In summary, after many years of very slowly progressive keratoconus, over a 14-month period the patient displayed remarkable changes in her corneal tomography. The steepest K changed from 63.7D to 71.5D in the right eye and from 65.8D to 78.1D in the left eye. Corresponding changes were noted in the Kmax values as well as in the anterior and, less dramatically, the posterior elevation (Table 1). After discussing the risks and benefits of corneal collagen crosslinking, the patient opted in favor of the procedure.

**3. Discussion**

Progression of keratoconus after menopause is generally

uncommon.<sup>1</sup> Age-related differences in human corneal biomechanical properties have previously been reported,<sup>10,11</sup> and it has been proposed that the resistance to keratoconus progression observed with aging may be due to physiological collagen crosslinking that is similar to the age-related changes in corneal stromal collagen biomechanics.<sup>12,13</sup> Given the relative resistance of the aged human cornea to keratoconus progression, our case of a 51-year-old postmenopausal patient exhibiting rapid disease progression following HRT is particularly intriguing.

Estrogen levels in the blood have previously been implicated in alterations to corneal anatomy. Specifically, the fluctuation of estrogen levels during the menstrual cycle, pregnancy, and abortion has been associated with changes in corneal thickness.<sup>14-16</sup> Corneal curvature has been reported to increase in pregnancy.<sup>17</sup> Moreover, case reports describe keratoconus progression or post-Laser-assisted in situ keratomileusis (LASIK) ectasia during pregnancy<sup>3,18</sup> and after IVF treatment.<sup>9</sup>

The extensive clinical data linking both endogenous and exogenous estrogens with altered corneal structure have prompted investigators to

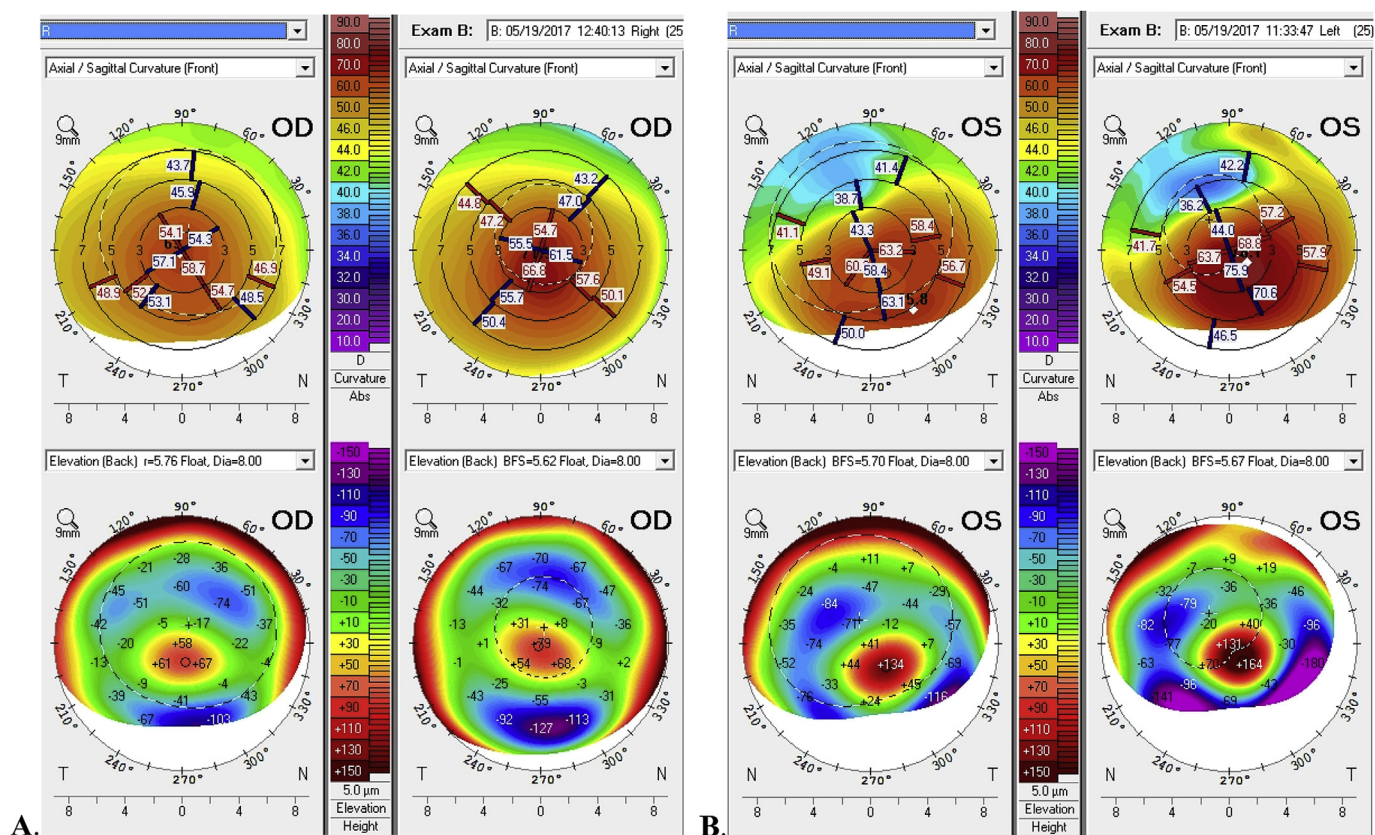


Fig. 2. Tomography exam (Pentacam) comparing the progression in the Axial/Sagittal Curvature (Front) and in the Posterior Elevation observed over 14 months (first and last exams shown). (A) Right eye and (B) left eye.

evaluate the effect of estrogens on corneal tissue *in vitro*. Spoerl and colleagues evaluated the changes in corneal biomechanical parameters induced by incubation of 12 fresh porcine corneas with  $\beta$ -estradiol for seven days.<sup>6</sup> The investigators reported that the incubation of porcine corneas with  $\beta$ -estradiol resulted in increased corneal thickness and, importantly, to a reduction in corneal stiffness compared to the control. These findings corroborate the role of estrogen as a modulating factor for corneal biomechanical stability.

Hormone receptors for estrogens, progesterone, and androgens are located in the nuclei of various human corneal cells such as stromal keratocytes, and epithelial and endothelial cells.<sup>19,20</sup> After the hormone binds its respective receptor, the newly-formed complex hormone-receptor acts as a transcription factor to regulate gene expression. The modulation of the synthesis of proteins, which are subsequently released into the extracellular matrix, changes the mechanical properties of the cornea.<sup>21</sup> Estrogens increase corneal distensibility as a result of their action on collagens through (i) the production of matrix metalloproteinases (MMP) and (ii) the direct or indirect (via prostaglandins) activation of collagenases.<sup>22,23</sup> These proteinases, acting on proteoglycans, change the viscoelasticity of the cornea by reducing the cohesion among collagen fibers.<sup>6</sup> Furthermore, proteinases modify corneal flexibility via stimulation of the synthesis of glycosaminoglycans that augment the tissue water binding capacity.<sup>24,25</sup>

Interestingly, the Collaborative Longitudinal Evaluation of Keratoconus Study (CLEK) reported no difference in the progression of keratoconus in relation to the hormone status of the patients aged 49–58 years.<sup>4</sup> Key limitations of the CLEK study, however, included the fact that the slow progression of keratoconus, commonly seen in this age group, may have compromised the detection of changes linked to sex and hormones. Furthermore, the findings may have been confounded by the fact that the study population defined as “hormone-active” represented a heterogeneous grouping of naturally hormone

active patients, patients at < 1 year following cessation of menstruation, and patients taking HRT. Finally, a subset of patients transitioned from being “hormone-active” to “hormone-inactive” during the study period.<sup>4</sup>

Previous studies have established that keratoconus may continue to progress beyond the age of 30,<sup>26</sup> yet the rate of progression observed in our 51-year-old patient is exceptionally high. It is important to acknowledge that atopy, and eye rubbing in particular, has been associated with keratoconus progression.<sup>27</sup> Although our patient was experiencing symptoms of allergic conjunctivitis, this is unlikely to be the primary cause of her disease progression given that she denied having rubbed her eyes.

#### 4. Conclusion

HRT is an extremely common therapeutic approach for alleviating the symptoms of menopause. The case reported herein implicates HRT in driving keratoconus progression, at least in this patient, and highlights the potential of estrogen levels in the blood to influence corneal biomechanics. Further studies are certainly required to fully delineate the effect of estrogen on keratoconus progression.

#### Patient consent

Written informed consent was obtained from the patient to publish case details.

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None.

## Conflicts of interest

The authors have no financial interest to disclose.

## Authorship

All authors attest that they meet the current ICMJE criteria for Authorship.

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