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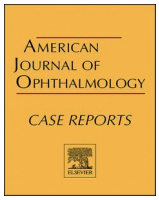

Possible association of keratoconus progression with gender-affirming hormone therapy: A case report

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ABSTRACT

Purpose: To present a case of keratoconus progression following gender-affirming hormone therapy.
Observations: A 28-year-old male-to-female transgender patient with potential past ocular history of subclinical keratoconus presented with subacute worsening myopia of both eyes (OU), 4 months after initiation of gender-affirming hormone therapy. A diagnosis of keratoconus was established based on slit-lamp exam and computerized corneal tomography. Notable indices were central corneal thinning and inferior steepening OU with maximum corneal curvatures of 58.3 D of the right eye (OD) and 77.7 D of the left eye (OS) and thinnest corneal thickness of 440 μm OD and 397 μm OS. After 8 months of continued hormone therapy, the patient's keratoconus continued to progress and thus corneal crosslinking was recommended and performed.
Conclusions: Keratoconus progression and relapse has been suggested to have an association with sex hormone changes. We report a case of keratoconus progression following gender-affirming hormone therapy in a transgender patient. Our findings continue to support a correlative relationship between sex hormones and corneal ectasia pathophysiology. Further studies are needed to determine causality and to investigate the utility of screening corneal structure prior to the initiation of gender-affirming hormone therapies.

1. Introduction

Keratoconus (KC) is a disease characterized by progressive corneal ectasia and thinning. Diagnosis can be made clinically at a point when these structural changes induce refractive errors that become increasingly progressive and difficult to correct. Central corneal thinning and inferior corneal steepening can be readily apparent on slit lamp examination as the disease progresses. In recent decades however, the introduction of computerized topographical and tomographical analysis of the cornea has allowed for earlier detection of ectasia and have become invaluable tools in the early diagnosis of KC. Placido disk-based topography has provided the ability to detect subtle changes in the corneal surface curvature. Scheimpflug tomography introduced three-dimensional imaging and brought about indices such as those to characterize posterior corneal curvature and corneal thickness elevation maps. Refinements to these imaging techniques as well as innovation with novel approaches continues to be developed.[1]

Historically, treatment options were limited to contact lenses and corneal transplantation.[2] KC is still a major reason for penetrating keratoplasty in developed countries. Click or tap here to enter text.[3] In the past two decades however, the minimally invasive procedure of corneal crosslinking has revolutionized management.[4–6] Nevertheless, morbidity remains high as crosslinking does not fully reverse vision loss and relapses may still occur.[5] Therefore, vision can best be preserved by early diagnosis and elucidating risk factors for KC development or progression.

The etiology of KC is incompletely understood. However, it is thought to be multifactorial, with the most established risk factors being both genetic and environmental: family history of KC, personal history of connective tissue or atopic disorders,[7] oxidative stress,[8] and microtrauma from eye rubbing[9]; per a review by Sugar and Macsai.[10] Recently, sex hormone changes have been implicated as well. Reports of KC progression during times of high estrogen have been published: in pregnancy,[11–13] *in vitro* fertilization (IVF),[14] and menopausal hormone replacement therapy.[15] Additionally, it has been observed that higher estrogen levels in men and lower testosterone levels in women appear to positively correlate with parameters of corneal ectasia.[16] We add to the literature by reporting a case of likely KC progression in a transgender

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patient undergoing gender-affirming hormone therapy, a clinical vignette not previously documented in existing publication to date as demonstrated by Pubmed all-fields search criteria of "keratoconus + hormone + transgender" for articles published within the last 10 years.

2. Case report

A 28 year-old male-to-female transgender patient with mild ametropia presented to optometry for subacute development of decreasing visual acuity OS > OD. Medical history was significant for initiating gender-affirming hormone therapy 4 months prior (estradiol and spironolactone). There was no personal or family history of known corneal disease. Manifest refraction was found to be plano/-0.50/x040 OD and −1.50/-0.25/x133 OS, correctable only to 20/30 OU. This refraction was similar to the last documented refraction from 9 years prior, which was +0.25/-0.50/x170 OD and −1.25/-0.25/x145 OS. However, the patient was able to correct to 20/20 OU at that time. Slit lamp exam was significant for faint Vogt's striae OS. Zeiss Atlas (Oberkochen, Germany) Placido disk-based topography was subsequently performed, revealing inferior corneal steepening OU with steepest curvature of 48.06 D ×120 OD and 61.22 D ×047 OS. Given these findings, referral for further work up by ophthalmology was requested.

At initial ophthalmology evaluation, the above manifest refraction and exam findings were confirmed. Further studies with Oculus Pentacam (Wetzlar, Germany) Scheimpflug tomography were performed. Maximum corneal curvatures (K_{max}) were 58.3 D OD and 77.7 D OS with heat maps illustrating steepness concentrated inferotemporally OU (Fig. 1), consistent with that shown by topography. Astigmatism was 7.5 D OD and 10.5 D OS. Thinnest corneal thickness (TCT) was 440 μm OD and 397 μm OS located slightly inferotemporal to the central cornea OU (Fig. 1). Anterior and posterior corneal elevation at TCT locations was 56 μm/106 μm respectively OD, and 70 μm/113 μm respectively OS (Table 1).

Initial management with contact lenses was recommended, however at follow-up 7 months later, the patient revealed non-compliance with contact lenses. The patient's hormone therapy regimen had also progressed to include progesterone in addition to the prior estradiol and spironolactone. BCVA was 20/25-1 OD and 20/40 OS. Tomographic indices of K_{max} and TCT were relatively unchanged from prior, however, average pachymetric progression across all corneal meridians appeared to have increased with index values advancing from 2.77 to 2.86 OD and 4.43 to 5.13 OS (Table 1). At this point, corneal crosslinking was recommended and later successfully performed.

Of note, while no diagnosis of KC had been established prior to the initiation of hormone therapy, there were also no documented corneal topographical or tomographical analyses prior to those performed above.

3. Discussion

Sex hormone effects on corneal structure and biomechanics are well established. Changes in corneal thickness during the menstrual cycle[17,18] and pregnancy[19] have been known for decades. Estrogen, progesterone, and androgen receptors have been shown to be present in the cornea and other ocular structures.[20] Particularly, there appears to be evidence of higher estrogen and androgen receptor expression in the corneas of KC patients.[21] *In vitro* studies have demonstrated estrogen's pro-ectactic effects on corneal biomechanics: (1) promoting water retention and therefore separation of collagen fibers via glycosaminoglycans, and (2) reducing stiffness by degradation of extracellular matrix via matrix metalloproteinases and collagenases.[22] In addition to these direct effects, indirect effects of estrogen on stimulating pro-inflammatory cascades associated with the severity of KC have also been described.[23] Less is known about a potential role for progesterone, and limited data thus far have not revealed any significant differences in tissue receptor expression or plasma progesterone levels between KC and normal corneas.[16,21]

Interestingly, Zhao et al. describe a statistically significant correlation of higher plasma estrogen levels in men with higher K_{max} and of lower plasma testosterone levels in women with lower TCT.[16] Though the study was limited by the cross-sectional design and the lack of further exploration regarding gender distinction, our case report supports this correlation by describing KC progression in a biological male after exogenous therapy raising estrogen levels (i.e. estradiol) and reducing testosterone activity (i.e. spironolactone).

Despite these *in vitro* and cross-sectional correlations between estrogen and KC, a longitudinal association between circulating plasma estrogen levels and KC remains less established and poorly described. The prospective Collaborative Longitudinal Evaluation of Keratoconus (CLEK) Study found no association between KC progression and hormone status in subjects aged 48–59 years.[24] However, significant limitations of the study have been discussed by the authors themselves as well as others.[11,14,15] These primarily include the heterogeneity of the "hormone-active" population studied, infrequent surveys (once annually) of hormone status, and a large shift in perspective on hormone therapy practices during the study period. For example, the "hormone active" group consisted of women with highly variable levels of "hormone activity": those with monthly menses, those 11 months following

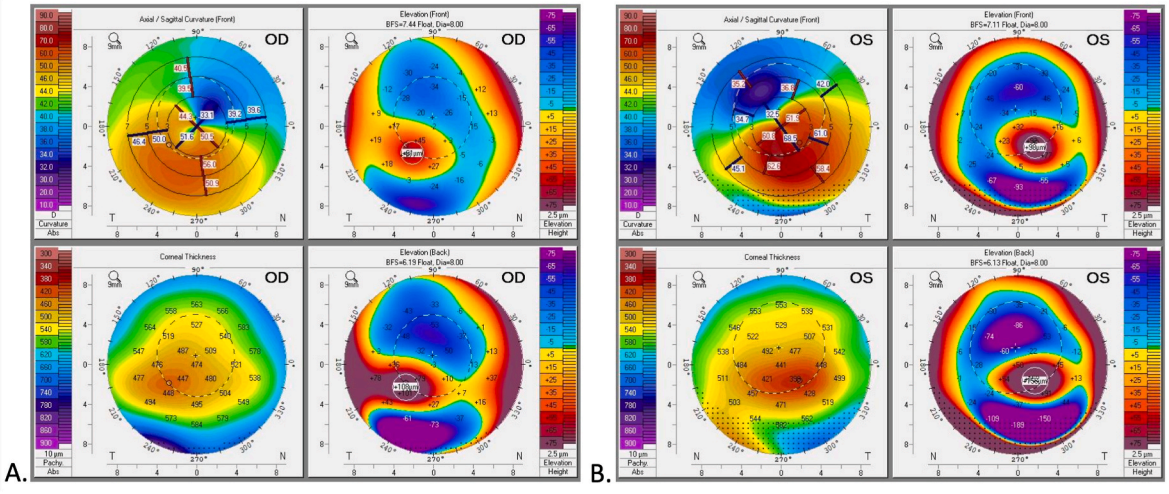

Fig. 1. Scheimpflug corneal tomography (Oculus Pentacam) status post 5 months of hormonal therapy. Heat maps show anterior inferotemporal corneal steepening, central-to-inferotemporal corneal thinning, and congruent elevation changes over anterior and posterior surfaces (A) OD and (B) OS.

Table 1
Notable measurements from Scheimpflug corneal tomography (Oculus Pentacam) at initial evaluation, follow up, and after corneal cross-linking for both eyes.

OD						
Encounter	Astigmatism (D)	Maximum corneal curvature (D)	Thickness at thinnest corneal location (μm)	Anterior corneal elevation at thinnest location (μm)	Posterior corneal elevation at thinnest location (μm)	Average pachymetric progression index value
Initial Ophthalmology evaluation	7.5	58.3	440	56	106	2.77
8-months follow up	7.2	59.3	441	56	109	2.86
6-months status post corneal cross-linking	6.9	59.4	443	–	–	–

OS						
Encounter	**Astigmatism (D)**	**Maximum corneal curvature (D)**	**Thickness at thinnest corneal location (μm)**	**Anterior corneal elevation at thinnest location (μm)**	**Posterior corneal elevation at thinnest location (μm)**	**Average pachymetric progression index value**
Initial Ophthalmology evaluation	10.5	77.7	397	70	113	4.43
8-months follow up	7.7	75	409	72	134	5.13
7-months status post corneal cross-linking	4.5	76	412	–	–	–

cessation of menses, those who recently initiated low-dose exogenous hormone therapy, and those on long-term high-dose hormone therapy. This variability was amplified when the Women's Health Initiative published results in 2002 that suggested potential harmful consequences from hormone therapy.[25,26] This resulted in a subsequent decrease in hormone therapy trends between 2002 – 2003,[27] during which the CLEK study was being conducted (2000–2004). Since the CLEK study, evidence has been limited to case reports and small cohort studies to suggest KC progression or corneal ectasia in high estrogen states of pregnancy,[11–13] IVF treatment,[14] and menopausal hormone therapy.[15]

The growing amount of evidence, to which our case report contributes, suggests the need for further large prospective studies to examine the effect of exogenous sex hormones on KC progression and development. While advances in diagnostic detection of KC have been made and continue to develop, sub-clinical detection will not occur without indication for screening. More evidence is necessary to determine if screening and documentation of corneal structure prior to the initiation of hormone therapies is indicated. A major limitation to our case report is the lack of advanced corneal structural analysis prior to the patient initiating hormone therapy. Thus, we cannot exclude the possibility of sub-clinical KC prior to therapy. However, clinical suspicion suggests that this is likely given the patient's documented history of ametropia.

Gender affirming hormone therapy in transgender patients is also an emerging issue in the medical community that calls attention to a unique patient population. Hormone therapy in these populations may present a disparate risk of KC progression than that of menopausal hormone therapy or IVF treatment. One reason is that increased age may confer protective resistance to ectasia. Demographic studies have noted that gender dysphoria typically arises within the first decade of life, and gender affirming treatment is sought in the next 10–20 years.[28] Opposite estrogen's effect, increasing age stiffens the cornea.[29,30] Accordingly, corneal changes in KC have been shown to stabilize with age, in a similar manner to corneal crosslinking treatment.[31] Another reason for possible disparate risk of KC progression in this population may be due to biological gender differences. Most studies on hormone therapy and KC progression have described these changes in biological women.[15] Pro-estrogen and anti-androgen therapies may increase KC progression to a different degree in biological males, such as in our case report. An interesting question is whether an opposite, protective, effect on corneal stability occurs with biological females receiving pro-androgen therapy.

In summary, this case report adds a clinical example of pro-estrogen and anti-androgen activity to the described positive correlation of such hormone activity with corneal ectasia. More studies, particularly looking at corneal structural data in patients before and after receiving hormone therapies may further elucidate this correlation. This may assist in determining if there is a role for the screening and/or risk assessment of corneal ectatic disease prior to the initiation of hormone therapies.

Patient consent

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

Authorship

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

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Declaration of competing interest

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