RETROSPECTIVE ANALYSIS OF COMORBIDITIES IN A SELECT KERATOCONIC POPULATION

by

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This paper is submitted in partial fulfillment of the requirements for the degree of

Doctor of Optometry

Ferris State University
Michigan College of Optometry

May, 2013

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Has been approved

May, 2013

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Doctor of Optometry Senior Paper

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ABSTRACT

Background: Keratoconus is a progressive corneal degeneration of an unknown etiology characterized by thinning of the corneal stroma, corneal protrusion, and increased myopia and irregular astigmatism. Genetic, biochemical, and histopathologic contributions to disease presentation and progression are under investigation, with existing evidence supporting contributions by each of these factors toward keratoconus development. Though several conditions have been shown to have strong associations with keratoconus, this disease usually presents in isolation. In this work, we investigate the prevalence of comorbid factors within a small population of known keratoconus patients as well as provide a thorough review of current literature on the disease. *Methods:* In this retrospective study, keratoconus patient records at the Michigan College of Optometry clinic were analyzed and all encountered comorbidities were tallied. The prevalence rates of these diseases within this population were then compared to known general prevalence rates. *Results:* Due to confounds inherent in experiment design, retrospective analysis does not allow for inferences of direct correlation or causation of any of the encountered comorbidities within our population. However interesting associations between the pathological processes regulating keratoconus and those of glaucoma and metastatic disease are worth consideration and warrant further investigation. *Conclusions:* This work, though rudimentary, does present some interesting information and inclusion of this data into some larger study may allow for future analysis of comordities found in keratoconus patients that can more accurately be compared to the general population.

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I. INTRODUCTION

Keratoconus is the most common primary ectasia (1) and is characterized by progressive, non-inflammatory, bilateral, asymmetric thinning of the corneal stroma. As the tissue thins and weakens, it can no longer maintain a regular shape against the force of the intraocular pressure of the eye, resulting in conical corneal protrusion, high myopia, irregular astigmatism presentation, and decreased vision. (1,2,3)

The purpose of this paper is two-fold: firstly, to investigate a noticed anecdotal clinical trend toward an increase in comorbid factors among keratoconus patients via retrospective investigation, and secondly, to provide an in-depth literature review highlighting known comorbidities associated with the disease, and the current suspected etiology and pathophysiology of keratoconus.

1. Epidemiology

Estimates on the incidence and prevalence of keratoconus vary, though the most commonly sited estimations are 1 per 2,000 and 54.5 per 100,000 respectively. (1-3) There is no definite gender preference in keratoconus. (1,2) Studies published on the matter have been largely conflicting, with some showing no difference in the prevalence of the disease between genders, (1) and others an increased prevalence among males or females. (1) Keratoconus is known to affect all ethnicities, (1,2) with some studies showing an increased prevalence among those of Asian decent. (1)

2. Clinical Features

The onset of keratoconus occurs most commonly around the time of puberty. The disease progresses until the third or fourth decade of life, at which time it generally stabilizes. (2)

Symptoms and clinical signs are highly variable and depend on the stage of disease progression. (2) In early keratoconus, refractive findings such as difficulty achieving an expected level best corrected visual acuity, increased myopia, an observable "scissors" reflex upon retinoscopy, and/or increased against-the-rule astigmatism may guide the astute practitioner to suspect the presence of keratoconus. Slit lamp examination findings which may present later in the disease process include visible thinning of the corneal stroma, iron deposition in the basal corneal epithelium near the base of the cone (Fleisher's ring), vertical folds in the deep stroma and Decemet's membrane (Vogt's striae), an oil-droplet (Charleux) sign upon retro-illumination post dilation, and prominent corneal nerves. (2) Rarely, breaks in Decemet's membrane may occur leading to acute, painful, corneal edema – a condition known as corneal hydrops. (1,2)

External signs, those observable without magnification, tend to be seen in progressed cases of keratoconus and include a V-shaped deformation of the lower lid upon downgaze (Munson's sign) and the formation of a sharply focused beam of light on the nasal limbus when more diffuse light is incident temporally(Rizzuti sign). (1,2)

3. Diagnosis, instrumentation, and classification

Diagnostic criteria for keratoconus vary between practitioners and there is no set of standard measures used to classify the presence or severity of the disease to date. (1)

Differential diagnoses for keratoconus include other corneal ectasisas and dystrophies that feature similar clinical findings and include pellucid marginal degeneration, Terrien's degeneration, and keratoglobus. (1,2)

Many classification schemes for keratoconus have been proposed, (1) though gross morphology of the cone is the most commonly used method clinically for qualifying the disease. *Nipple* cones are smaller in size (< 5mm) and are central or paracentral in location, with those paracentral nipple cones most commonly found infero-nasally. (1) *Oval* cones are typically larger and are located paracentrally to peripherally. Oval cones most commonly present infero-temporally and are considerably more challenging to manage with contact lenses. (1)

Confirmatory testing occurs most usually via imaging by computerized corneal topography; an auxiliary that has gained widespread acceptance in clinical practice throughout the past twenty years. (2,4) Early or so-called forme fruste cases of keratoconus may show subtle elevation of the posterior corneal surface without anterior topographical changes. (4) In these instances, computer-assisted topographers are particularly valuable tools in the early detection of or the screening for keratoconus. (2,4) Three topographic features are of particular note in keratoconus: 1) Focal steepening in the area of the cone, generally having dioptric values greater than 46.0, with surrounding

concentric zones of decreasing power. 2) Asymmetry between the inferior and superior aspects of the midperipheral cornea resulting in an inferor-superior asymmetry index values greater than 1.4D. 3) Angling of the hemimeridians as displayed by a "bow-tie" pattern oriented greater than 20-30 degrees from vertical midline consistent with an increase in against-the-rule astigmatism. (4)

Other measures of interest in keratoconus diagnosis and research include corneal asphericity, anterior and posterior surface aberrometry, corneal hysteresis, and corneal pachymetry. Detailed discussion of these items deviates from the primary aims of this paper, the reader may see APPENDIX A for a brief overview of their relevance.

4. Etiology and pathogenesis

Clinically noticeable features of keratoconus stem from aberrations in form and function at the cellular and molecular level. Though the etiology of these changes is still being clarified and quantified, promising research regarding possible hereditary influences in disease presentation, abnormalities in protease inhibition, and possible correlations with other collagen vascular disorders is currently underway.

4.1 Histopathology

Three histological changes that have been identified as characteristic of keratoconus are ferritin accumulation within the basal layer of the corneal epithelium, breaks in Bowman's layer, and thinning of the corneal stroma. (1,2)

The iron deposition in keratoconus occurs within the basal epithelial cell cytoplasm. (5) Several theories exist as to how the iron deposition leading to a clinically noticeable Fliesher's ring occurs. One thought is that the metal accumulation results from the degeneration and movement of basal epithelial cells toward Bowman's layer, and subsequent build up of ferritin particles between these cells. (1) Alternatively, the existence of errors in iron metabolism within the epithelium has also been proposed. This theory implies a down-stream effect of alterations of the interactions between the corneal epithelial cells and the underlying stroma, possibly playing a role in stromal thinning. (5) Other changes noted within the corneal epithelium in keratoconus include an increase in intracellular space between basal cells, and decreased basal cell density. (1,5)

Breaks in Bowman's layer are thought to occur via a generalized weakening of the lamina's collagenous constructs, (3) and may be visualized as Z-shaped interruptions filled with stromal collagen bundles which have risen up through these fissures. (1)

The exact histological changes resulting in stromal thinning in keratoconus are complex and multifaceted. They provide insights into the pathogenesis of the disease, and the mechanisms behind these changes have yet to be discovered. A decreased number of keratocytes, fibroblast degradation, decreased amounts of and changes in the organization of lamellae, gross thinning of lamellae due decreased bonds (cross links) between and within their constituent collagen fibrils, and an uneven distribution of collagen fibrillar mass have all been observed in the stromata of keratoconus patients. (1,3)

Descemet's membrane is usually unaffected in keratoconus except in the rare

instance of corneal hydrops. (1,2) The corneal endothelium too, is generally unchanged in keratoconus. (1,2)

4.2. *Genetics*

Strong evidence exists to support a hereditary component to keratoconus presentation, with the majority of family studies and twin studies suggesting an autosomal dominant mode of inheritance with variable expression. (1,2) Investigations using genetic analyses via linkage studies of families with keratoconus have found multiple loci associated with the disease. (1) Allocation of cause for disease presentation to specific gene mutations would be a premature assertion as of yet, however, as studies to date investigating point mutations have been largely conflicting. (1)

4.3 Biochemical factors

Biochemical changes leading to the overall degeneration found in keratoconus are still being elucidated. Loss of stromal collagen fibrils has been linked to differences in the structural properties of collagen in keratoconus versus normal corneas, increases in proteolytic enzyme activity, down-regulation of proteolytic enzyme inhibitors, increases in pro-inflammatory markers, decreases in anti-inflammatory molecules, and improper induction of keratocyte apoptosis. (1-3, 5)

Structural differences in collagen types XIII, XV, and XVIII have been noted between normal eyes and those with keratoconus. (1) It has been suggested that these

structural variations may contribute to abnormalities in corneal wound healing observed in the disease. (1)

The activity of collagenasas and gelatinases are of particular interest in the study of keratoconus. These enzymes belong to a family of proteins known as matrix metalloproteinases (MMP's), so-named as they contain a zinc atom within their active site. (6) Study of the activity of MMP's has been confounded largely by the enzymes' regulation and state of activation, as they exist in an inactive zymogen form and become functional upon proteolytic cleavage, and subsequent changes in their tertiary structures. (6) Conflict exists between studies as to the role of the majority MMP's in keratoconus, though strong evidence exists for increases in matrix-type metalloproteinase 1 in keratoconus. (6)

More uniformly between studies, molecules that inhibit MMP activity have been found in lesser amounts in eyes with keratoconus compared to normals, specifically, α-1-antichymotrypsin, α-2-macroglobulin, and RNA leading to the formation and expression of α-1 proteinase inhibitor. (6)

Over-expression of specific pro-inflammatory markers, such as inerleukin-6, intercellular adhesion molecule 1, and intercellular adhesion molecule 6 by up to 40 times greater than normal has been demonstrated in eyes with keratoconus versus their disease-free counterparts. (1) On the opposite side of this same coin, anti-inflammatory molecules such as interleukin-10 have found to be expressed in amounts eight times lower in contact lens wearing keratoconus patients compared to contact lens wearing, healthy myopes. (1)

The loss of anterior stromal keratocytes may be related to an increased expression of interleukin-1 (IL-1) receptors on the cells' surface. IL-1 is thought to play a role in the induction of apoptotic cell pathways in keratocytes . IL-1 receptor expression in the cells of keratconus eyes has been shown to be approximately four times that of those belonging to normal corneas (1,3). Furthermore, some studies have found IL-1 release to increase upon epithelial trauma. (1) Though merely speculative, this may account in part for the association of keratoconus with eye rubbing, contact lens wear, and atopy. (1)

4.4 Associated conditions/findings

Keratoconus presents most commonly in isolation. (1-3) Though there have been many reports of other diseases associated with keratoconus, only a handful of these have been found to have some significant correlation. A table from Rabanowitz (2, p298) quite excellently displays the diseases that had been found concurrently with keratoconus up to the date of the article's publication. Readers should refer to this source for more information.

A few diseases and clinical features have been found to have a significant association with keratoconus. These include Down's syndrome, Osteogenesis imperfecta (OI), Ehlers-Danlos syndrome subtype VI (ED), Leber's congenital amaurosis, atopy, joint hypermotility and mitral valve prolapse. (1,2)

Down's syndrome has been shown to have an association with keratoconus that is

10-300 times higher than the general population. (1) Some speculate that the increased rate of blepharaitis in this population, 46% of Down's syndrome individuals, may lead to an increase in eye-rubbing which may be the actual predisposing factor for development of keratoconus. (1)

Leber's congenital amaurosis, a rare genetic disorder with a spectrum of symptoms depending on penetrance, has also been linked to increased eye rubbing. This may contribute to this disease's association with keratoconus. (1)

Of particular interest are those disorders or findings linked with connective tissue dysfunction, including ED, OI, joint hypermotility, and mitral valve prolapse as the connection with these disorders hints at some common structural malfunction of collagenous tissues. One study found that compared to 7% of normal subjects, 58% of keratoconus patients that require surgery have mitral valve prolapse. (2) Conflicting studies on this association and the proposed link of keratoconus to joint hypermotility have also been published, however. (1,2)

5. Treatment and Management

Treatment modality depends on the severity of presentation of keratoconus and early on in the disease process, spectacle correction may achieve an acceptable best-corrected visual acuity. (1,2,7) Contact lenses are the considered the mainstay of therapy, however, representing treatment of choice for 90% of keratoconus patients. (7)

Incipient cases may be successfully managed with soft hydrogel or silicone

hydrogel lens designs, but gas permeable contact lenses (GPC's), are far and away a much more commonly utilized and successful option. (1,2,7) Traditionally, small diameter GPC's with an apical touch fit were the predominant approach to vision correction in keratoconus. (7) The use of lens designs having multiple peripheral base curves following this same fitting philosophy has steadily increased in popularity since their introduction. (7) Large diameter scleral and semi-scleral designs, which do not follow the apical-touch fitting scheme, are being used as a treatment option with increasing frequency, touting improved comfort and possibly a lower risk of corneal scarring. (7) No randomized clinical trial has been carried out to assess which fitting philosophy or contact lens design performs the best, however. (1)

Newer hybrid lens designs such as *SoftPerm* (Ciba Vision, Duluth, Georgia, USA) and *Synergeyes* (SynergEyes, Carlsbard, CA, USA) have also been used successfully in keratoconus management, but represent a vast minority of fits. (1) Though used infrequently, so-called "piggyback" lens fitting, the practice of fitting a GPC over a soft hydrogel or silicone hydrogel lens, may be used in instances of intolerance of the foreign body sensation associated with GPC wear but for which optimal visual acuity cannot be achieved with soft lenses or spectacles alone. (1,2)

Surgical procedures exist for those advanced cases that cannot be successfully managed with contact lenses. Full-thickness corneal transplantation, penetrating keratoplasty (PKP), is the most commonly used surgical option. (1,2,7) It is estimated that 12%-20% of keratoconus sufferers ultimately elect for corneal transplantation. (7)

Alternative surgical and parasurgical treatment options such as partial thickness corneal transplantation, intra-corneal ring segment implantation, intraocular lens implantation, and corneal collagen cross-linking are becoming increasingly more frequent treatment modalities. (7)

Corneal collagen cross-linking (CXL) shows particular promise in slowing the progression of keratoconus. (7) Following epithelial debridement in the central 6-7mm of the cornea and application of a topical 0.1% riboflavin solution, the area is exposed to 370nm ultra-violet radiation for 30 minutes. (1,7) Photosensitization of riboflavin results in the creation of reactive oxygen species that induce the formation of covalent bonds, referred to as "cross-links," between collagen fibrils within the corneal stroma. (1) These changes improve corneal structural integrity and increase corneal rigidity. (1,7) Long-term studies have shown minimal risk associated with the procedure and have found improved best-corrected visual acuity, flattening of keratometry values, and decreased rates disease progression. (1,7) Though still only used in clinical trails in the United States, results of CXL therapy are encouraging and the procedure exists as a standout prospect for future management of keratoconus. (7)

II. METHODS

Subjects

All patient information was obtained following application for, and subsequent approval of the inclusion of human subjects in our study as granted by the Institutional Review

Board of Ferris State University. Only those patients who had previously signed a consent clause authorizing use of information about their case for the purposes of education or research by Michigan College of Optometry (MCO) were included in our sample.

Our sample population was selected by searching "active" Michigan College of Optometry clinic records for those patients positive for International Classification of Diseases (ICD-9) codes correlating to keratoconus, or corneal transplantation. Those records fitting the later of these two criteria were then examined for a positive history of keratoconus prior to PKP. For institutional record-keeping purposes, an "active" chart is one for a patient who has been seen within the past seven years and who has not been lost to follow-up.

Patients designated as keratoconus suspects were not included in our analysis. Other subjects excluded from our study were those whose charts were inactive, whose charts were unable to be located, and those who did not consent for the use of their information by MCO for the purposes education and research.

The total sample size of this study is n=86, with 36 subjects being female, and 50 being male. 21 subjects had undergone PKP. Ages of included subjects, as calculated relative to the date of authorship of this paper, range from 9-80 years. The mean and median age for all subjects is 48.34 years and 49 years, respectively. The mean and median age for female subjects is 48.67 years and 49 years, respectively. The mean age of male subjects is 49.2 years, and the median age for males is 49 years.

Collection procedure

After those records to be included in the study were gathered, the ocular and systemic health history of each patient record was examined and the findings noted. All conditions on all history forms (not simply the most recent) for each patient were counted one time per patient, as a comorbidity. As well, all concurrent non-refractive diagnoses made were included, one time per incidence per patient, in our study. Each nominal value, or disease condition, encountered in our sample was listed and all recurring instances of this condition added to a tally in spreadsheet form. (see APPENDIX B)

Instrumentation

As this is a retrospective analysis of existing records, no particular formal instrumentation was used specific to this study. Some variance exists regarding the medical equipment (e.g. slit lamp biomicroscope make and model) utilized in each patient exam leading to the diagnosis of keratoconus. A copy of the MCO clinic patient health history form used in each included patient record, is provided for reader consideration. (see APPENDIX C)

Statistical procedure

No statistical measures inferring causation and correlation are appropriate, given this study's design. Statistical information will be presented as prevalence values for each comorbidity found within our total sample of keratoconus patients as well as male and

female only prevalences. For the purposes of purely anecdotal comparison, any disease listed as a comorbidity within our population for which a reliable prevalence within the general population is known will have this metric listed and the source of this parameter available for reader review and consideration.

III. RESULTS

The calculated prevalence within our sample population for each encountered co-morbidity is listed in Table 1. General population prevalence for a portion of the encountered co-morbidities can be found in Table 2. Those diseases included in Table 2 were those for which the authors could find reliable prevalence measures.

TABLE 1
Prevalence of Encountered Comorbidities

Disease	Frequency	Percent prevalence	Frequency among females	Percent prevalence among females	Frequency among males	Percent prevalence among males
Anemia	1	1.2	0	2.8	0	0
Arthritis	13	15.1	5	13.9	8	16.0
Athsma	9	10.5	3	8.3	6	12.0
Cogan's dystrophy	1	1.2	1	2.8	0	0
Corneal guttata	2	2.3	2	5.6	0	0
Coronary Artery Disease	1	1.2	0	0	1	2.0
Depression	8	9.3	4	11.1	4	8.0
Diabetes Mellitus	6	6.9	2	5.6	4	8.0
Eczema	1	1.2	0	0	1	2.0
Epiretinal membrane	3	3.5	0	0	3	6.0
Floppy eyelid syndrome	1	1.2	0	0	1	2.0
Glaucoma	2	2.3	0	0	2	4.0
Hypercholesterolemia	13	15.1	6	16.7	7	14.0
Hypertension	25	29.1	5	13.9	20	40.0
Hypothyroidism	3	3.5	2	5.6	1	2.0
Irritable bowel syndrome	1	1.2	0	0	1	2.0
Lattice degeneration (retinal)	8	9.3	3	8.3	5	10.0
Macular hole	2	2.3	2	5.6	0	0
Multiple myeloma	1	1.2	0	0	1	2.0
Operculated hole	3	3.5	1	2.8	2	4.0
Psoriasis	2	2.3	0	0	2	4.0
Rosacea	1	1.2	1	2.8	0	0
Salzmann's degeneration	4	4.7	4	11.1	0	0
Seasonal allergies	18	20.9	13	36.1	8	16.0
Skin cancer (unspecified)	1	1.2	1	2.8	0	0
Sleep Apnea	1	1.2	0	0	1	2.0
Vernal limbal keratoconjunctivitis	3	3.5	0	0	3	6.0
Vitreal tuft	2	2.3	2	5.6	0	0

TABLE 2

*General Prevalence of Select Comorbidities**

Disease	Percent prevalence	Percent prevalence among females	Percent prevalence among males
Arthritis	22.1[8]	24.1[8]	19.4[8]
Asthma	12.6[8]	14.0[8]	11.1[8]
Coronary artery disease	6. 3[8]	4.7[8]	8. 3[8]
Depression	16.6[9]	-	-
Diabetes Mellitus	8.6[8]	8.0[8]	9.2[8]
Eczema	10.7[10]	-	-
Epiretinal membrane	5.3[11]	-	-
Glaucoma	1.75-1.96[12]	-	-
Hypercholesterolemia	13.0[13]	-	-
Hypertension	24.3[8]	23.5[8]	25.1[8]
Hypothyroidism	0.3[14]	-	-
Irritable bowel syndrome	10.0-15.0[15]	-	-
Lattice degeneration (retinal)	7.1-10.0[16]	-	-
Macular hole	0.3[17]	-	-
Multiple myeloma	0.67[18]	-	-
Psoriasis	0.91[19]	-	-
Rosacea	0.5-10.0[20]	-	-
Seasonal allergies	7.1[8]	8.1[8]	6.0[8]
Sleep apnea	20.0[21]	-	-

* References listed in superscript

- Information unavailable

Diseases found to have a higher prevalence in our population include asthma in males, glaucoma, hypercholesterolemia, hypothyroidism, macular hole, multiple myeloma, psoriasis, and seasonal allergies.

IV. DISCUSSION

Regarding comparison of those diseases known to be more prevalent in keratoconus patients to our sample, the results are contradictory. For the prevalence of conditions associated with atopy, asthma was lower in our total sample and within females in our sample (10.5% and 8.3%, respectively) compared to known values (12.6% and 14.0%), while the prevalence of asthma among the males in our sample was found to

be higher than general measures (12.0% versus 11.0%). Seasonal allergies were found to have a higher prevalence compared to known values for our total sample, as well as the male only and female only sects of our sample. (See Table 1 and Table 2 for more information)

The higher prevalence of glaucoma within our sample compared to known values raises cause for consideration. Keratoconus and glaucoma have both been shown to be associated with reduced corneal thickness as well as low corneal hysteresis measures. (3) At least one study has found a correlation between the magnitude of hysteresis decrease and the severity of keratoconus. (22) This same study, however, found no correlation between hysteresis values of keratoconus patients with glaucoma compared to those keratoconus patients without this comorbidity. (22)

Unfortunately, no members in our sample were found to have a connective tissue disease that has been shown to be associated with keratoconus.

The original anecdote of possible disease association that spurred this study was a possible increase in metastatic disease prevalence among keratoconus patients. Though this study did include one case of multiple myeloma, no other metastatic conditions were noted. Transforming growth factor-β (TGF-β) and its correlated pathway has been shown to limit epithelial cell proliferation in the early stages of oncogenesis. (23) Curiously, TGF-β has been found to be a tumor-promoting factor later on in oncogenesis by inducing an epithelial to mesenchymal transition. (23) Increases in TGF-β pathway markers have been found in some instances of severe keratoconus. (24) Though more

investigation regarding the exact role of this pathway in both oncogenesis and keratoconus progression need be done, the tenuous association of this cytokine with both of these disease processes may point to some commonalities in their pathological processes.

Several issues regarding experiment design became apparent late during the process of this project. The most notable of these is the lack of a control. Though not requisite for the type of study attempted (observational retrospective), more inferences regarding relative prevalence could have been gleaned by using case controls: gathering a number of patients without keratoconus from the MCO patient database who visited the clinic during the same seven year time period. Comparison of the keratoconus sample to a case control sample would reflect more accurate variations in prevalence findings of diseased subjects versus some general population because variables such as temporal, environmental, nutritional, and socio-economic differences would be greatly minimized.

The second most notable inaccuracy with this report stems from calculation of prevalence within our small sample. Broadly speaking, prevalence values for rare diseases found within a small sample tend to be falsely high relative to the prevalence within the general population. This confound is one that the authors of this study have taken into careful consideration and one that we at this time call to the reader's attention.

Other potential problems with experiment design include non-uniform diagnostic criteria between practitioners, usage of current patient age versus age at time of

diagnosis, and gross heterogeneity of our sample relative to those in the various studies of overall disease prevalence used for anecdotal comparison.

Expounding on the last point above, the age and sex distribution of our sample does not mirror that for each study selected for comparison. As well, our sample is one of convenience, without a case control the differences mentioned above (temporal, environmental, nutritional, and socio-economic) become uncontrolled variables.

Unfortunately, though the authors would have appreciated the ability to gather case controls and make the findings of this study more statistically sound and relevant for reader consideration, temporal issues regarding the length of time required for augmenting experiment design and obtaining university approval for this proposed change did not permit this correction.

V. CONCLUSION

It is the authors' hope that despite these flaws, the reader can, at least on a superficial level, gain some information from this review and study. Though disease prevalence within our population of keratoconus may not be directly comparable to known prevalence measures or disease associations, the connection between corneal hysteresis measures in keratoconus and glaucoma as well as possible connections between certain active cell pathways in both keratoconus and metastatic disease raise some interesting pathological processes to consider.

Also, the authors hope that the raw data may serve as a stepping-stone for later research. Possibly our sample of keratoconus patients may be included with others to increase the sample size, improve the reliability of prevalence measures, and to aid in constituting a final sample that is more representative of the general regional or national population.

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APPENDIX A

CORNEAL ASPHERICITY, ABERROMETRY, PACHYMETRY, AND HYSTERESIS

A. CORNEAL ASPHERICITY, ABERROMETRY, PACHYMETRY, AND HYSTERESIS

Asphericity (Q) is a parameter qualifying the magnitude and direction of deviation a given curved surface has relative to a perfect sphere (Q=0). Asphericity values of normal subjects with no history of refractive surgery have a range indicative of a prolate-ellipsoid shape, with a mean asphericity value of Q= -0.29 (+/-) 0.09 according to one study (4). This same study found eyes of keratoconus patients to exhibit increased prolateness, with mean asphericity values of Q = -0.65 (+/-) 0.27 and Q = -1.18 (+/-) 0.32 in keratoconus grade I and keratoconus grade II groups, respectively. (4)

Analysis of both anterior and posterior corneal surface aberrations proves quite useful in the detection of keratoconus. Primary coma and coma-like root-mean-square aberrations are found to be present in significantly greater amounts in the analyses of both the anterior and posterior surfaces of corneas affected by keratoconus. (4)

Hysteresis is an indirect indicator of overall corneal rigidity that is preferred over traditional quantifying parameters as it is more indicative of the visco-elastic physical state of the cornea and measures can be performed in vivo. (3) An averaging of several studies done by Ambekar et al. observed the mean hysteresis values for normal and corneas in keratonconus to be 10.66 (+/-) 1.96 mmHg and 8.51(+/-) 1.87 mmHg, respectively. (3) Analysis of corneal hysteresis may prove to be useful diagnostic tools for keratoconus in the future, as findings for both normal and diseased eyes are consistent

across studies and hysteresis measures are found to lower predictably with disease progression. (4)

Studies focusing on pachymetric analysis of corneas of keratoconus patients have found significant differences in both central and minimum corneal thickness relative to normal eyes. Furthermore these differences become more marked with advancement of the disease. (4) Though central thickness measures via single-point pachymetry commonly find keratoconic corneas to be thinner than healthy eyes, multi-point analysis using more sophisticated imaging systems such as those based on Scheimpflug photography or ocular coherence tomographers allowed for more detailed and accurate estimates of corneal thickness. (4)

APPENDIX B

COLLECTION DATA: PATIENT PARAMETERS AND ENCOUNTERED COMORBIDITIES

COLLECTION DATA: PATIENT PARAMETERS AND ENCOUNTERED COMORBIDITIES

	gender	age	pkp	cataracts	cogans	guttata	VLK	floppy eyelid	ERM	macular hole	vitreous tuft	lattice	retinal hole, tear or detachment	glaucoma suspect	glaucoma	major depression	seasonal	asthma	HTN	hyper-cholesterolemia	CAD	DM	hypothyroidism	anemia	rosacea	eczema	psoriasis	arthritis	skin cancer	multiple myeloma	ulcer/IBS	sleep apnea
1	female	73	OD	1						1	1	1				1	1			1									1			
2	female	56	OU																	1		1	1		1							
3	female	37	OS														1															
4	male	68																1	1	1												
5	female	79	OU														1		1													
6	male	22																														
7	male	29																														
8	female	48														1				1			1					1				
9	female	56															1															
10	male	57																	1	1												
11	male	34																														
12	female	74			1	1																										
13	male	80	OD											1																1		
14	male	22																														
15	female	34																														
16	female	35										1					1															
17	male	48																	1													
18	male	55											1				1								1			1				
19	female	71	OD																1													
20	female	44															1											1				
21	male	61	OU																1	1												
22	male	42																	1													
23	female	49																1														
24	female	47																														
25	male	37	OS																													
26	female	31	OS																													
27	female	57														1												1				
28	male	61					1																									
29	female	50															1															
30	female	52				1																										
31	male	46										1		1		1			1													
32	female	38															1															
33	male	43	OD															1	1							1						
34	male	36	OS																													
35	female	65																		1		1										
36	male	55												1					1			1										
37	female	61																														
38	male	66																1														
39	male	42																	1													
40	male	57																					1									
41	male	66							1			1																1				
42	female	46		1																												
43	female	49	OU																													
44	female	24																														
45	male	50																	1								1					
46	male	58	OU															1	1	1												
47	male	58										1																1				
48	female	24																														
49	female	57		1																												
50	male	64					1																									
51	male	35																				1										
52	female	63	OS							1							1							1								
53	male	40																														
54	male	30															1															
55	male	17															1															
56	male	42						1								1			1	1								1			1	
57	female	27																														
58	male	68	OU												1		1		1									1				
59	female	66																	1	1												
60	male	36																														
61	male	62																	1	1	1	1										1
62	male	64	OD											1					1													
63	female	63											1					1										1				
64	female	33																														
65	male	46	OU												1		1	1				1										
66	female	35															1															
67	male	9										1																				
68	female	54														1	1	1	1													
69	male	56	OU													1												1				
70	female	29									1	1					1															
71	male	65							1				1							1												
72	male	41																														
73	male	30																														
74	male	47																	1													
75	male	55	OD											1																		
76	male	47	OU																													
77	male	50																	1								1	1				
78	male	58	OU															1	1													
79	male	58										1																1				
80	female	24																														
81	female	67		1													1		1	1								1				
82	male	64					1																									
83	male	66							1							1			1													
84	female	34																														
85	male	22																														
86	male	42																	1													
	TOTALS	48	21	4	1	2	3	1	3	2	2	8	3	5	2	8	18	9	25	13	1	6	3	1	2	1	2	13	1	1	1	1

APPENDIX C

MICHIGAN COLLEGE OF OPTOMETRY PATIENT HEALTH HISTORY FORM

MICHIGAN COLLEGE OF OPTOMERY PATIENT HEALTH HISTORY FORM

University Eye Center

FERRIS STATE UNIVERSITY · MICHIGAN COLLEGE OF OPTOMETRY

Patient Health Information

Name	Social Security Number	Today's Date
Address, City, State, ZIP	Home Telephone Work Telephone	Birth Date

Thank you for taking your time to carefully complete the patient health information form. This information will be reviewed by the doctor during your examination. All information provided will be held in strict confidence.

PERSONAL EYE HISTORY

- Have you had your pupils dilated? Y N If yes, were there any problems? _____
- Do you wear glasses? Y N If yes, how old are your glasses? _____
- Does your occupation or any hobbies/recreational activities require the use of safety eyewear? Y N
- Date of last complete eye exam _____ Name of eye doctor _____
- Have you ever worn contact lenses? Y N Do you now wear contact lenses? Y N
  What type of contact lenses? Hard/RGP Soft Extended Bifocal
- Are you planning to get new glasses or contact lenses today? Y N Maybe
- Are you interested in learning about laser vision correction or non-surgical vision correction? Y N Maybe

Please note any family members with the following conditions.

EYE CONDITIONS	YES	NO	UNSURE	RELATIONSHIP
Blindness				
Glaucoma				
Macular Degeneration				
Other				

Name of Vision Insurance

_____

PERSONAL MEDICAL HISTORY

- List medications you are currently taking (prescription and over-the-counter). _____
- Do you have any allergies to medications? Y N If yes, please explain. _____
- List major illnesses, injuries, and surgeries you have had. _____
- Date of your last physical exam _____ Are you pregnant / nursing? Y N
- Name and office location of your medical doctor(s) _____

FAMILY MEDICAL HISTORY

Please note any family members with the following conditions.

MEDICAL CONDITIONS	YES	NO	UNSURE	RELATIONSHIP
Arthritis				
Cancer				
Diabetes				
Heart Disease				
High Blood Pressure				
Other				

Name of Medical Insurance*

_____

*Medical insurance will only cover your visit if there is a medical reason such as loss of vision, headaches, eye redness, eye pain, eye itching, eye burning, glaucoma, cataracts, etc.

SOCIAL HISTORY

- What is your occupation? _____
- Do you use a computer at work or at home? Y N
- List your hobbies/recreational activities. _____
- Do you drive? Y N If yes, do you have visual difficulty when driving? Y N
- Do you use tobacco products? Y N If yes, what type/amount/how long? _____
- Do you drink alcohol? Y N If yes, how often? _____
- Do you use illegal drugs? Y N
- Have you ever been exposed or infected with the following: HIV? Y N TB? Y N

REVIEW OF SYSTEMS

Do you now have or have you ever had any of the following health problems?

PROBLEMS	YES	NO	IF YES, PLEASE EXPLAIN
• Eyes			
• Eye injury or eye pain			
• Loss of vision			
• Blurred vision			
• Tired eyes			
• Redness			
• Itching			
• Burning			
• Sandy or dry eyes			
• Excessive tears (watery eyes)			
• Vision disturbance (spots, halos, light flashes)			
• Light sensitivity / glare			
• Double vision			
• Glaucoma			
• Cataract			
• Macular degeneration			
• Diabetic retinopathy			
• Amblyopia			
• Eye turn (eso- or exotropia)			
• Keratoconus			
• Learning disability			
• Constitutional (fever, weight loss)			
• Ears, Nose, Mouth, Throat (sinus, chronic cough, etc)			
• Respiratory (asthma, emphysema, etc)			
• Cardiovascular (high blood pressure, vascular disease, etc)			
• Gastrointestinal (diarrhea, constipation, ulcers, etc)			
• Genitourinary (genitals, kidney, bladder)			
• Muscles/Bones/Joints (arthritis, etc)			
• Endocrine (diabetes, thyroid, etc)			
• Psychiatric (anxiety, depression, etc)			
• Blood/Lymph (anemia, high cholesterol, etc)			
• Allergic/Immunologic (hay fever, lupus, etc)			
• Skin			
• Neurological (headaches, multiple sclerosis, etc)			

I am responsible for payment at the time of each visit for all services provided by Michigan College of Optometry not covered by an insurer. My signature serves as a "signature on file" for claim processing and for release of medical information to my insurance carrier(s).

_____

signature of patient or person authorized to sign for patient

I authorize Michigan College of Optometry to use photographs or information concerning my case in the interest of education or research.

_____

signature of patient or person authorized to sign for patient