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Prevalence of keratoconus in patients with vernal keratoconjunctivitis in a population serviced by the St John Eye Hospital in Johannesburg, South Africa.

This Mmed dissertation is written in submissible format. It is to be submitted to the South African Ophthalmology Journal (SAOJ), see the appendix for the submission format.

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Abstract

Background: Keratoconus (KC) is a bilateral asymmetrical disease of the cornea that results in severe thinning of the cornea leading to a cone formation of the cornea. Vernal keratoconjunctivitis (VKC) is an allergic eye condition that is associated with the development of KC. The aim of this study is to observe the extent to which KC is present in VKC.

Methods: A cross-sectional study design was utilised. It took place in the St John Eye Hospital, in Johannesburg, South Africa. Eighty patients and 160 eyes were included. The presence of, and the type of VKC was observed. All KC patients were classified according to sex, age and whether clinical or subclinical KC was observed.

Results: This study yielded a 58% prevalence of KC. Of this, 44% were males and 56% were females. The age category represented as age 10-15 had a 51% KC prevalence. Subclinical KC had a 71% prevalence whilst clinical KC had a 29% prevalence.

Conclusion: This study highlights the high prevalence of KC and subclinical KC. It advocates for the development and use of screening protocols for KC in VKC, which would ultimately assist in early disease detection and thus result in an improved quality of life for those affected.

Key words: Prevalence, keratoconus, vernal keratoconjunctivitis, early detection, screening.

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1. Introduction

Keratoconus (KC) is a progressive bilateral corneal condition characterized by asymmetrical thinning and steepening of the cornea which causes a significant reduction in vision.[1] It is associated with a common allergic eye condition called vernal keratoconjunctivitis (VKC), which often affects children and young adults.[1] The adverse impact of late detection of this condition is experienced both by the patient and by the healthcare system. For the patient, this emanates in terms of an increased risk of visual impairment which naturally affects their quality of life, and furthermore, where this risk of severely reduced vision could be managed, this requires an extensive and often costly medical intervention. For the healthcare system, a lack of early detection requires more extensive and costly medical expertise to cure or manage a process that could be more efficiently handled with early detection. It is well understood that VKC is not only a risk factor for the development of KC but also causes significant progression of the disease.[1] Unfortunately, once clinical findings of KC can be identified on the slit lamp examination, then the aim of treatment is to prevent progression of KC. If KC is advanced at the time of diagnosis, then more invasive methods are the only option to manage and potentially improve vision.

In the developing world, particularly in Africa, access to good ophthalmic healthcare is not always readily accessible, often resulting in late presentations to healthcare facilities. In this study, we investigated the prevalence of KC in patients presenting to our hospitals with a clinical diagnosis of VKC. VKC is a chronic bilateral allergic disease that mostly affects children and young adults.[1] It is a self-limiting disease, usually resolving completely during its natural course. In its severest form, it can result in extensive damage to the cornea and adjacent structures resulting in irreversible vision loss. These sequelae can have a massive effect on one's quality of life. There are three main types of VKC – tarsal, limbal and a mixed type. These are defined in the table below.

Table I: Types of vernal keratoconjunctivitis

VKC type	Definition
Tarsal	Conjunctival papillary hyperplasia of the tarsal plate with giant papillae >1mm in diameter[2,3]
Limbal	The presence of subconjunctival nodules with or without superimposed white dot formation called Horner Trantas dots[2,3]
Mixed	Characterised by the evidence of Tarsal and Limbal VKC simultaneously[2,3]

VKC = vernal keratoconjunctivitis.

The symptoms of VKC range from itchy eyes, epiphora and photophobia to hyperpigmentation and thickening of the eyelid margins and severe damage to the cornea.[1] On examination, patients may present with discharge as well as tarsal and or limbal conjunctival papules.

In severe forms of VKC, the cornea is significantly affected. This is a result of a complex type I and type IV hypersensitivity reactions.[1] These reactions initiate and drive the inflammatory cascade in VKC.[1] This inflammatory cascade involves several cells, with the dominant cell type being eosinophils.[1] Eosinophils and their proinflammatory cells that are active in VKC are known to particularly cause damage of varying degrees of the cornea.[1] This targeted corneal damage begins with the activation of numerous enzymes, matrix metalloproteinase nine (MM9) and Eosinophil Cationic Protein to name a few.[1,4] These enzymes then lead to a breakdown of corneal epithelium which initiates an inflammatory cascade that leads to further corneal damage.[1]

One particularly well-known association of VKC that affects one's vision is KC.[1] Keratoconus results in severe thinning of the apical cornea leading to a cone formation of the cornea as well as the development of corneal irregularity.[5,6] It is important to note that in the beginning, before the clinical corneal manifestation of KC, biomechanical changes of the cornea occur.[7] It is at this point that subclinical KC can be identified. Keratoconus can be classified as clinical or subclinical. It is widely recognised that VKC has a strong association with KC, with the association being so high that some authors state that KC is a complication of VKC.[5,8,9] In addition to the allergic predisposition associated with VKC, the mechanical act of eye rubbing is known not only to cause KC but to aid in its progression.[1] In particular, patients with VKC have been known to have steeper keratometry measurements and more severe forms of KC.[1,10] Keratoconus is a word with origins in the Greek language.[11] Kerato means cornea and Konos means cone.[11] Until recently, it was thought of as a non-inflammatory disease; however, the evidence of the activated cytokines present suggests otherwise.[5,6] Keratoconus results in steeping of the cornea with significant reduction in vision and it is the most common cause of corneal transplants in developing countries.[6]

Keratoconus is known to be more prevalent in hot and sunny climates which is typical in South Africa.[2] This and the association with atopy and eye rubbing are thought to be one of the reasons that Africa has a noticeably higher prevalence of KC of 7.9% compared to the global prevalence of 0.13%.[5,6] Technological advancement in corneal imaging has helped improve risk factor identification for the development of KC. This would ultimately result in earlier detection of KC, therefore improving the impact of this disease on the patient and also the healthcare system and leading to a reduced need for corneal transplants in an already resource-limited demographic, Africa. It is valuable to understand the prevalence of KC in VKC. The objective of this study was to examine the incidence of KC observed in patients with VKC at a hospital in Johannesburg, South Africa.

2. Methods

A descriptive cross-sectional study was done to observe the extent of KC in a sample of patients with VKC. From December 2023 to February 2024, 80 consenting patients (i.e. 160 eyes) aged 10 – 30 years with any type of VKC were sampled from the ophthalmology clinic at St John Eye Hospital, Johannesburg. The patients ranged in age from 10 years to 30 years. All patients had to sign a written consent form after receiving an information sheet about the study. All patients under the age of 18 had to sign an assent form in addition to the written consent provided by a parent or legal guardian. Patients were excluded if they had corneal scarring from causes other than previous hydrops or previous intraocular surgery. Patients with already confirmed KC were also excluded.

Each patient was examined and had an anterior segment slit lamp examination that included an uncorrected Snellen chart assessment of their visual acuity. Each patient then had an Oculus pentacam® scan performed on both eyes. The presence or absence of KC or subclinical KC was then determined based on the results. The clinical and subclinical classification of KC for this study are provided in Table II. All participants needed to have met the criteria for clinical or subclinical KC shown in Table II provided below.

Table II: Classification of clinical and subclinical keratoconus

Parameter	Clinical keratoconus	Subclinical keratoconus
Visual acuity	6/12 or worse	6/9 or better
Slit lamp examination	• Apical corneal scarring • Full thickness corneal scar from previous hydrops; and/or • The presence of Fleischer ring • Munson sign • Rizzuti sign • Scissor reflex	• No clinical findings of KC
Pentacam parameters	• K values ≥ 48.0D • CCT < 500µm • Inferio-superior asymmetry index; and/or • Bowtie pattern with skewed radial axes • D value > 1.6 and < 2	• K values ≥ 47.0D • CCT < 500µm • Inferior-superior asymmetry index; and/or • Bowtie pattern with skewed radial axes • D value > 2

K = keratometry, CCT = central corneal thickness, D = total deviation value.

Even with all the technological advances in ophthalmology, currently, there is not one single investigative metric that can without a doubt differentiate early KC from the normal cornea. However, using various corneal pentacam parameters aid in the diagnosis of KC and importantly subclinical KC.[12,13] The pentacam parameters analysed as per Table II were the anterior and posterior corneal elevation maps, keratometric values, the thinnest location and the D value. Slit lamp findings as well as age and sex were included in the data collected.

Permission to conduct the study was granted by Chris Hani Baragwanath Academic Hospital (CHBAH), Johannesburg. Ethical clearance was obtained from the Human Research Ethics Committee, University of the Witwatersrand (M230672).

3. Results

Of the 80 patients (and 160 eyes) sampled, 51% (n=41) were females. The largest age group was 10 – 15 years, 60% (n=48). All patients were Black Africans, Table III. Of the 160 eyes examined, tarsal VKC was the main type (81%), followed by the mixed type (18%) and then the limbal type (1%), Table III.

Keratoconus was present in 58% (n=93 eyes) of all the eyes examined. Of these, the majority, 71% (n=66 eyes) were subclinical, Table III.

Table III. Study results

Characteristic	Category	n	%
n (patients)		80	100
Demographics			
Age category (years)	10 – 15	48	60
	16 – 20	19	23
	21 – 25	8	10
	26 – 30	5	6
Sex	Female	41	51
	Male	39	49
Race	Black African	80	100
n (eyes)		160	100
Type of VKC	Limbal	1	1
	Mixed	29	18
	Tarsal	130	81
KC within VKC	Present	93	58
	Absent	67	42
KC type within VKC (n=93 eyes)	Clinical	27	29
	Sub-clinical	66	71

VKC = vernal keratoconjunctivitis, KC = keratoconus.

Keratoconus was more prevalent in patients with tarsal VKC (n=73 eyes; 78%), with the subclinical type being the majority (n=48 eyes). Keratoconus was seen in only 18 eyes of those with mixed VKC, Table IV.

Table IV: Keratoconus type distribution within VKC type

KC type	VKC type			
	Tarsal	Limbal	Mixed	**Total**
Clinical	25	0	2	**27**
Sub-clinical	48	0	18	**66**
Total	**73**	**0**	**20**	**93**

VKC = vernal keratoconjunctivitis, KC=keratoconus.

Of the 93 eyes where KC was observed, females accounted for 56% (n=52 eyes) and males, 44% (n=41 eyes). In both males and females, subclincal KC was the most common type, Table V.

Table V: Prevalence of keratoconus by sex (n=93 eyes)

Presence of KC and type: n (%)	Sex		
	Male	**Female**	**Total**
KC observed	41 (44)	52 (56)	93 (100)
Clinical	*14 (52)*	*13 (48)*	*27 (100)*
Subclinical	*27 (41)*	*39 (59)*	*66 (100)*

KC = keratoconus.

Amongst the different age categories, KC was observed in 51% of the 10 – 15 year age group. The prevalence decreased with increasing age category. The 10 – 15 year age group also had the highest prevalence of subclinical KC (n=40 eyes, 61%), Table VI.

Table VI: Prevalence of keratoconus by age category (n=93 eyes)

Presence of KC and type: n (%)	Age category (years)				
	10 -15	16 – 20	21 -25	26 – 30	Total
KC observed	47 (51)	20 (22)	16 (17)	10 (11)	93 (100)
Clinical	*7 (26)*	*11 (41)*	*3 (11)*	*6 (22)*	*27 (100)*
Subclinical	*40 (61)*	*9 (14)*	*13 (20)*	*4 (6)*	*66 (100)*

KC = keratoconus.

4. Discussion

The findings of this study show a high incidence of KC in VKC this is highlighted and discussed below. There were slightly more females than males in the patients sampled for this study with most being 10 – 15 years of age. All patients were Black Africans. St John Eye Hospital is located in Soweto, Johannesburg, South Africa and provides healthcare services to the population of Soweto who are predominantly Black Africans.[14]

The primary objective of this study was to determine the prevalence of KC in patients with VKC. As mentioned earlier, this is important to understand because the effects of KC are preventable and the outcomes of management are favourable to both the patient and the health system if detection occurs early. This study showed that more than half of all the patients had KC, where KC was observed in 93 of the 160 eyes examined, equating to a prevalence of 58%. This prevalence is not similar to what has been described in literature where the prevalence of KC is lower.[5] This high prevalence immediately confirms the importance of being cognizant of the presence of KC when assessing patients with VKC.

It is important to delineate KC into clinical and subclinical types as subclinical KC can be managed if detected early to prevent the morbidity of clinical KC. The majority (71%) of the patients with KC in this study had subclinical KC. The high prevalence of subclinical KC found in this study probes the thought that we may have significantly underestimated the prevalence and thus the impact KC has in this community and in the developing world.

With regards to the type of VKC, the available literature on VKC associated KC shows that KC occurs more frequently in the tarsal and mixed types of VKC.[1] This study is comparable to that of literature as KC was observed mainly in those with tarsal VKC followed by the mixed type. Both were associated with clinical (tarsal VKC) and subclinical (tarsal and mixed VKC) KC. Previous studies reported that the mixed type of VKC predisposes individuals to more KC, this finding demonstrates a somewhat different outcome where the tarsal VKC had the most significant effect on the prevalence of both clinical and subclinical KC.[15] In this study, KC was not seen in those with limbal VKC. One way to interpret this is that the presence of limbal VKC, especially that with Horner trantas dot, is quite a noticeable finding for patients. Thus, patients are more likely to seek medical attention due to the negative cosmetic appearance one can have. However, because the pathology in tarsal VKC is concealed by the eyelids, patients only seek medical attention when the itching, photophobia and blurred vision become unbearable. It is important to note that all three types of VKC can present with itching; but, the likeliness of someone continuing to rub the eyes in an attempt to relieve the constant itching before

medical help is sought is higher in the tarsal type of VKC. In this delayed search for medical attention, the significant effect of eye rubbing has a head start in the damage it causes before patients become aware of a change in their vision.

When comparing the prevalence of KC by sex, keratoconus was more prevalent in females than in males. This finding is particularly insightful given that a meta-analysis of KC in Africa by Akowuah et al. indicated a higher prevalence of KC in VKC in males of 9.3% and 5.8% in females.[5] There is no consensus on any true gender predilection as there are various findings for males and females throughout the literature.[6] For medical practitioners, it is important to be aware of these findings and potentially test females earlier for KC when they present. However, this does not mean that males should receive any less attention as more than a third of all KC identified were observed in males. Encouragingly, in both sexes, subclinical KC was the commonest type making it possible to use less invasive treatment modalities.

Finally, it was important to understand the age groups where KC often occurs. The majority of KC, and in particular subclinical KC, was identified in the 10 – 15 year age group. This finding supports the literarture of KC starting in the first decade.[1] It also highlights the importance of screening patients within this age group with risk factors for KC. In the literature, it is known that KC tends to progress in the first two decades.[1] It is therefore important to note that the majority of the patients with subclinical KC in this study will progress to clinical KC and increase the burden on the already resource constrained health system. However, it is also encouraging to have identified more patients and at a younger age with subclinical KC than clinical KC. This finding is crucial in our approach to managing patients with KC. It shows that preventative protocols such as screening can and should be developed to early detect KC in patients with VKC. If patients with obvious risk factors are screened regularly, more subclinical KC can be diagnosed and thus the use of less invasive treatment modalities, like cross-linking which are significantly more available, can be utilised. Screening protocols will not only reduce the number of patients requiring full penetrating keratoplasty treatment, but it will also reduce the sequelae of KC.

5. Limitations

This study has been able show a noticeable incidence of KC in VKC in this population however, the study has faced certain limitations that must be acknowledged. Firstly, this study was of a small sample size therefore constraining the true incidence of KC in VKC. Secondly, there are different investigative metrics that can be utilized to determine the presence of subclinical KC. These limitations however, do not reduce the impact of the findings instead, they provide a platform that future studies can improve on.

6. Conclusion

Keratoconus is a disease that, if detected early, can be treated to prevent further sequelae to the patient and reduce the burden on the healthcare system. This study found a high prevalence of KC in patients with VKC presenting to St John Eye Hospital. In addition, majority of those diagnosed with KC had subclinical KC and were mostly young in age, within the first decade. In this study, females had a higher prevalence of KC than males.

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