**BioScientific Review (BSR)** Volume 4 Issue 3, Fall 2022

ISSN<sub>(P)</sub>: 2663-4198 ISSN<sub>(E)</sub>: 2663-4201

Homepage: https://journals.umt.edu.pk/index.php/bsr



Article QR



Frequency of Vernal Kerato-conjunctivitis (VKC) and its

Title: **Complications in Patients Presenting at District Headquarter** 

Hospital, Sheikhupura

Muhammad Awais Asghar<sup>1</sup>, Amina Muqaddas<sup>1</sup>, Kiran Iftikhar<sup>1</sup>, Shehrish

Author (s): Kamran<sup>2</sup>, Mishel Zainab<sup>3</sup>, Musa Ali Irfani<sup>4</sup>, Usman Ayub Awan<sup>5</sup>

<sup>1</sup>Department of Ophthalmology, District Headquarter Hospital, Sheikhupura, Pakistan **Affiliation (s):** 

<sup>2</sup>Department of Pathology, Shaukat Khanum Memorial Cancer Hospital and Research

Center, Lahore, Pakistan. <sup>3</sup>Mayo Hospital, Punjab, Pakistan.

<sup>4</sup>Department of Public Health, Margallah Hospital, Taxila, Punjab, Pakistan

<sup>5</sup>Department of Medical Laboratory Technology, The University of Haripur, Haripur,

Khyber Pakhtunkhwa, Pakistan

DOI: https://doi.org/10.32350/bsr.43.01

Received: April 08, 2022, Revised: June 04, 2022, Accepted: June 15, 2022 **History:** 

Asghar MA, Muqaddas A, Iftikhar K, et al. Frequency of Vernal Kerato-

conjunctivitis (VKC) and its complications in patients presenting at District Headquarter Hospital, Sheikhupura. BioSci Rev. 2022;4(3):18-

28. https://doi.org/10.32350/bsr.43.01

Copyright: © The Authors

This article is open access and is distributed under the terms Licensing:

of Creative Commons Attribution 4.0 International License

Conflict of

Citation:

Author(s) declared no conflict of interest Interest:



A publication of

The Department of Life Sciences, School of Science University of Management and Technology, Lahore, Pakistan

# Frequency of Vernal Kerato-conjunctivitis (VKC) and its Complications in Patients Presenting at District Headquarter Hospital, Sheikhupura

Muhammad Awais Asghar<sup>1\*</sup>, Amina Muqaddas<sup>1</sup>, Kiran Iftikhar<sup>1</sup>, Shehrish Kamran<sup>2</sup>, Mishel Zainab<sup>3</sup>, Musa Ali Irfani<sup>4</sup>, Usman Ayub Awan<sup>5\*\*</sup>

### **Article Info**

#### Abstract

Received:08-04-2022 Revised: 04-06-2022 Accepted:15-06-2022

## Keywords

allergen, allergic
eye disease,
papillae, shield
ulcer, Vernal
Keratoconjunctivitis
(VKC)

Vernal Kerato-conjunctivitis (VKC) is an allergic illness that affects the eyes and causes the inflammation of conjunctiva, which is commonly bilateral. If left untreated, it may lead to serious consequences such as redness, stinging, and watering of the eyes, resulting from papillae, Horner-Trantas spots, and punctate epithelial lesions. The current study aimed to determine the prevalence of VKC in the Out-Patient Department (OPD) of Ophthalmology at the District Headquarter Hospital, Sheikhupura. VKC was diagnosed in 40 individuals between May and June of 2021. The majority of them were young men who were less than 20 years old. Indeed, it was found that VKC is more prevalent in children and men. Around 57.5% of children in our study were boys, whereas 42.5% were girls. Almost every single one of them was less than twenty years of age. Among the various age groups, it was found that the age group (6-10 years, n=18) had the highest prevalence of VKC cases, followed by the age group (n=11) (1-5 years). To prevent patients from developing illness consequences that negatively impact their quality of life, VKC must be handled promptly and with diligent follow-up. To conclude, the current study found that VKC in Pakistan follows a pattern similar to other tropical nations, with male predominance and higher prevalence during infancy and puberty.

<sup>&</sup>lt;sup>1</sup>Department of Ophthalmology, District Headquarter Hospital, Sheikhupura, Pakistan

<sup>&</sup>lt;sup>2</sup>Department of Pathology, Shaukat Khanum Memorial Cancer Hospital and Research Center, Lahore, Pakistan.

<sup>&</sup>lt;sup>3</sup>Mayo Hospital, Punjab, Pakistan.

<sup>&</sup>lt;sup>4</sup>Community Health, Margallah Hospital, Taxila, Punjab, Pakistan

<sup>&</sup>lt;sup>5</sup>Department of Medical Laboratory Technology, The University of Haripur, Haripur, Khyber Pakhtunkhwa, Pakistan

<sup>\*</sup>Corresponding author: awaisasghar3@gmail.com

<sup>\*\*</sup>Co-Corresponding author: <u>Usman.ayub111@gmail.com</u>

#### 1. Introduction

Vernal Kerato-conjunctivitis (VKC) is a chronic ocular illness characterized by allergic inflammation of the conjunctiva. It is frequently bilateral and impairs the patient's daily activities. It is widespread throughout the world's tropical and subtropical climates [1]. It is defined by the presence of tarsal or limbal papillae on the tarsal conjunctiva that is often larger than 1mm in diameter and induces itching with photophobia, redness, watering, and a foreign body feeling. The patient must have experienced a comparable event at least once in the preceding six months.

VKC is more frequent in males, hot and humid climates, and regions with a higher allergen load in the air [2]. It has a detrimental effect on the patient's typical routine and renders them incapable to carry their everyday responsibilities. Seasonal changes aggravate VKC [3]. In chronic patients, the disease may result in a devastating loss of sight due to corneal problems or as a side effect of long-term medication use [2]. Corneal involvement in VKC is manifested by discomfort, irritation, and photophobia. The most frequent corneal problems found in individuals with VKC are punctate epithelial keratitis, corneal shield ulcers, and keratoconus. Punctuate epithelial keratitis can consolidate, resulting in severe epithelial erosion. Corneal shield ulcers are oval in form and have their lower boundary in the visual axis' top half. A scar resembling a subepithelial ring frequently noticed as evidence of a healed shield ulcer [4].

In Nigeria, VKC is the most prevalent conjunctival illness affecting children attending school or presenting in hospitals. These children are unable to engage in their favourite activities due to the risk of illness

progression, demonstrating its negative impact on their quality of life [5].

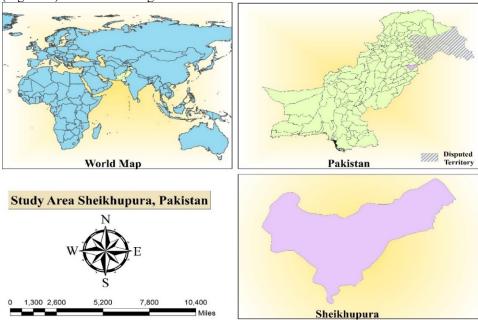
If VKC is not adequately and timely managed, it may lead to blindness [3]. Various authors have described it at different times as spring catarrh, circum corneal hypertrophy, recurrent vegetative conjunctiva, and verrucosa conjunctiva, thereby highlighting different aspects of the disease. Cobblestone papillae are those with sizes ranging from 7-8 mm [4]. On ocular examination, VKC is identified by the presence of hyperemia of the conjunctiva, the appearance of papillae (of varied sizes) in tarsal conjunctiva or the appearance of gigantic papillae in the limbal area [6]. It is a difficult-to-prevent but manageable allergic disease. Regular hand and face washing, avoiding extended sun exposure, avoiding dust and smoke, and refraining from touching or rubbing the eyes are a few disease preventative strategies. Medical therapy is required to regulate its clinical manifestations [7].

VKC is a common cause of hospitalization in children in various countries of Africa [8], Asia [9], and the Middle East [9], with an incidence of 5% observed in Chad and Dibouti for adolescents [10]. On the other hand, a study conducted in Pakistan revealed that 88% of early-onset cases were male [11]. However, in Pakistan, only a limited number of epidemiological studies on VKC have been undertaken so far. Moreover, its prevalence in the central region of the country has not been established by any study focusing on the most prevalent patient presentation. Thus, our study sought to determine the frequency with which patients with VKC present in the Out-Patient Department (OPD) of Opthalmology at District Headquarter Hospital, Sheikhupura based on their age group and presentation.

Additionally, we also examined the rate of VKC-related problems.

#### 2. Materials and Methods

The current study used a cross-sectional design. It included 40 participants with recurrent bilateral symptomatic VKC who had conjunctival papillae at the superior tarsus and/or limbus as a character trait of the disease, as well as symptomatic conjunctivitis symptoms such as itching, wetness, and redness. All of the participants gave their informed verbal consent to be a part of this study. The current study took approximately two months to complete, commencing from January 2022 February 2022. It was conducted at the Out Patient Department (OPD) Opthalmology at District Headquarter Hospital, Sheikhupura, Punjab, Pakistan (Figure 1). After obtaining the informed verbal consent of the participants or their parents/guardians, patients had a full eye examination regardless of gender and age. The exclusion criteria comprised the presence of infective keratitis and ocular problems such as glaucoma. Moreover, contact lens wearers and individuals unwilling to participate in the study were eliminated. VKC-related symptoms and indicators were recorded via a specifically created proforma. Visual acuity was assessed using Snellen's chart and slit-lamp examination, while intraocular pressure was determined using Goldmann's applanation tonometer. A 90D lens was used to investigate the fundus. Moreover, the prevalence and severity of VKC, as well as the connection between VKC and corneal involvement, were evaluated.



**Figure 1.** Map Highlighting the Study Area, That is, Sheikhupura City in Pakistan. This is One of The Most Populous Cities In The Punjab Province of Pakistan.

All of the obtained information was inserted into a pre-designed worksheet. SPSS software (version 21) was used to analyze the data. For categorical factors, such as gender and type of VKC, frequencies and percentages calculated. For quantitative factors, such as age, mean and standard deviation were calculated. The various types of VKC were sorted by age and gender to determine their significance and effect modifiers. The findings were depicted through tables and graphs. The analysis of the link between clinical parameters and the severity and progression of the illness was carried out using the Chi-Square test with a 95% confidence interval, while a p-value of less than 0.05 was declared statistically significant. Statistical analysis was carried out with the help of SPSS (version 21) and Microsoft Office 365.

#### 3. Results

A total of 40 individuals, 23 males and 17 females, were enrolled for this study. The mean age of the patients was 8.8 years (with a range of 3-20 years). Almost everyone of them was younger than twenty years of age. Among the various age groups, VKC cases were the most frequent in the age group (6-10 years, n=18), followed by the age group (1-5 years, n=11). However, a significant decrease in VKC instances was observed after ten years of age. Only two cases of VKC were identified in the 16-20 age range, as shown in Figure 2.

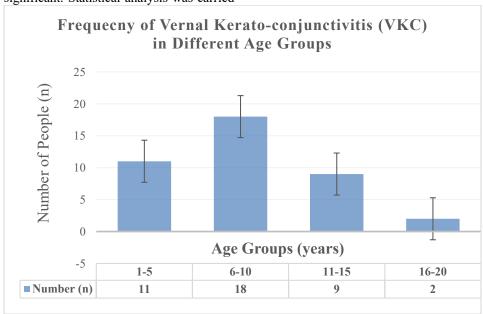


Figure 2. Distribution of Vernal Kerato-conjunctivitis (VKC) among Different Age Groups

The prevalence of VKC varied according to gender, with a greater frequency in the male population as compared to the female population. In the participants, about 57.5%

of the children were boys, with the remaining 42.5% were girls, as shown in Figure 3.

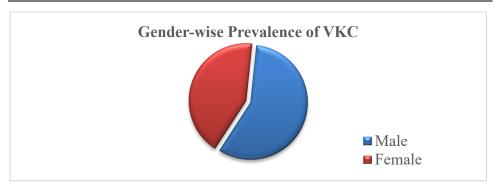


Figure 3. Gender-wise Distribution of Patients Presented with the Complaint of VKC

All patients expereinced severe itching, watering, and redness on their faces. Patients with VKC had limbal or tarsal

papillae present in all cases, with micropapillary identified in most people with the condition, as shown in Table 1.

Table 1. Frequency of different symptoms and signs of VKC among the participants

Clinical parameters	Degree of severity	Frequency	p-value
Itching	Mild	3(7.5%)	
	Moderate	5(12.5%)	0.002
	Severe	17(42.5%)	0.002
	Very Severe	15(37.5%)	
Watering	Mild	5(12.5%)	
	Moderate	11(27.5%)	0.001
	Severe	20(50%)	
	Very Severe	4(10%)	
Redness	Mild	7(17.5%)	
	Moderate	10(25%)	0.020
	Severe	18(45%)	
	Very Severe	5(12.5%)	
Papillae	None	13(32.5%)	
	Micro	22(55%)	<0.001
	Macro	3(7.5%)	< 0.001
	Giant	2(5%)	
<b>Horner Trantas Dots</b>	Absent	21(52.5%)	0.752

Clinical parameters	Degree of severity	Frequency	p-value
	Present	19(47.5%)	
Punctate Epithelial Erosion	Absent	39(97.5%)	< 0.001
	Present	1(2.5%)	
<b>Shield Corneal Ulcer</b>	Absent	39(97.5%)	<0.001
	Present	1(2.5%)	< 0.001
Keratoconus	Absent	40(100%)	
	Present	0(0%)	-

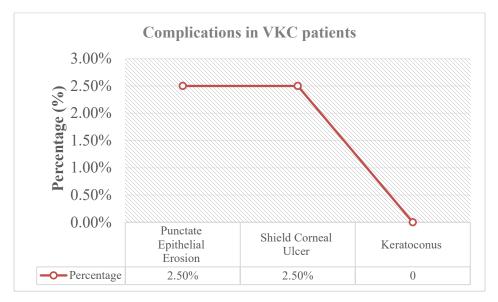


Figure 4. Frequency of Common Complications among VKC Patients

In comparison, the subsequent sequelae, such as punctate epithelial erosion, shield corneal ulcer, and keratoconus were unremarkable in the participants. The two most common complications observed in the children were punctuative epithelial erosion (n=1; 2.5%) and shield corneal ulcer (n=1; 2.5%). As depicted in Figure 4, there were no cases of keratoconus reported among the children, which remains a significant difference.

#### 4. Discussion

The current study showed that the frequency of VKC among patients presenting in the eye OPD of District Headquarter Hospital, Sheikhupura for a duration of two months (May-June 2021) was 40. It came with a male preponderance and the majority of patients were less than or equal to 20 years old. The current study included 23 male and 17 female patients. A previous study included 405 male and 63

female patients with an M:F ratio of 6.4:1 [2]. Leonardi and colleagues revealed an M:F ratio between 3.3 and 3.5 in two different observations, one of which was a multicentric research conducted in Italy [12, 13]. Another research also revealed comparable results, with an M:F ratio ranging between 4:1 and 2:1 [2, 3, 14]. Even though Ukponmwan claimed an M:F ratio of 1:1.3 in Nigeria [15]; however, another study from the same territory showed an M:F ratio of 1.27 [3]. The prevalence of VKC among male patients was confirmed in our study via its M:F ratio, which was consistent with the worldwide trend.

VKC is regarded as a childhood illness that often disappears during puberty. According to a study, the most common age range for VKC is 6-10 years of age(51.12%). This finding is consistent with a Ugandan study that determined the most common age of presentation with VKC to be between 5 and 9 years [16]. The youngest participant was three years old, while the oldest was twenty years old. Leonardi et al. [12] reported only 4% of patients over the age of 20 years with VKC. In contrast, Shafiq et al. [17] observed 6% of patients with VKC who were more than 20 years of age in a singlecenter hospital-based study conducted in Pakistan. According to a study, UV light and wind interaction may be significant factors. with wind enhancing susceptibility to allergens in dirt and pollen. Children are especially vulnerable since they are involve in outdoor activites, therefore, they are more exposed to different dirt and allergens[16].

Contrastively, the rate of VKC found in this study was less than that found by studies conducted in Nigeria (18.1%) [14], Mali (37.2%) [18], and India (18.2%) [19]. There is a possibility that the disparities are attributable to various environmental,

physiological, and genetic factors that all have a role in the development of VKC. Another plausible explanation for the above disparity in VKC rates is that it is attributable to the different age groups examined in each one of the above mentioned investigations. Earlier researches examined groups with participants below 15 years of age, which is nearer to the high-risk group for VKC since it typically manifests during the first years of life [15, 17]. On the contrary, this study involved participnts with ages up to 20 years, where the rate of VKC declines.

The most common presentation in this study was the one with severe itching, redness, and watering that made it hard for the patients to carry on with their normal routine activities. Most of the patinets were presented with mild and moderate grades of VKC in other studies [2, 20]. Additionally, patients reported experiencing a foreign body sensation, soreness, and a change in the colour of their eyes, which is consistent with the findings of the previous studies [14, 20]. All patients had papillae. Depending on the size, the majority had micropapillary, while 19 patients had Horner-Trantas dots. In another study, ocular signs of VKC including the prevalence of papillae were 100%, while 54% of patients were reported with Horner-Trantas dots [21].

VKC can produce a variety of corneal problems, all of which can result in impaired vision. This study included only one patient with punctuating epithelial erosions and one with corneal shield ulcer. None of the patients had keratoconus. Bonini et al. reported that 6% of patients experience irreversible vision loss due to corneal abnormalities and scarring [17]. In one study, people with corneal shield ulcers were found to be 3% of the total population [2]; although, a slightly higher incidence

was reported in two other studies, that is, 9.7% and 15.3%, respectively [12, 17]. Keratoconus seems to be an additional corneal disorder that can occur due to VKC [22]. In a prior study, keratoconus was detected clinically and with corneal topography in 6.2% of the patients [2]. Other studies found a very reduced prevalence of this problem, ranging from 0.5% to 2.1% [12, 17].

VKC is also associated with peripheral corneal neovascularization documented in different studies, albeit the extent of this problem has not been determined [4, 6]. This condition is characterized by chronic and persistent inflammation of the cornea that leads to damage to limbal stem cells and also their loss, which results in the conjunctivalization of the cornea [23]. Although Limbal Stem Cell Destruction (LSCD) is rare, it causes debilitating vision impairment [2]. Our study reported a relatively low incidence of corneal complications and associated visual loss because patients were presented to a district healthcare facility at an earlier stage of the disease. Contrastively, all preceding studies were conducted in tertiary care settings with a significantly greater patient load and consequently, a higher incidence of associated complications. VKC is a difficult-to-prevent but manageable allergic reaction [24]. The best approach to avoid contracting an eye infection is to wash the hands and face frequently, avoid the sun, prevent breathing in dust and smoke, and not rubbing eyes [7, 25, 26]. Moreover, pharmacological treatments are also critical for illness control [24, 26].

This study reported the incidence of VKC in the underdeveloped healthcare sector of Pakistan's outlying cities. Moreover, it also reported the prevalence of VKC in a city where no previous research had been undertaken on this delicate matter. Its

limitations included a small sample size and a single-centered analysis of data collected from only one district eye care facility, so the results may not adequately reflect the unique characteristics of patients treated at a community center. Another shortcoming of the current study was that only OPD patients were included. Keeping in view the findings of this study, it is strongly recommended that patients and parents be counseled regarding the recurring nature of the disease and the adverse side effects of an injudicious and prolonged corticosteroid treatment.

#### 5. Conclusion

Our study determined that VKC in Pakistan follows a pattern consistent with other tropical nations, marked with a male predominance and a greater prevalence of the disease throughout infancy and puberty. VKC is a bilateral eye condition that often manifests as itching, redness, and rubbing of the eyes. It is a chronic condition that requires close monitoring and patient compliance.

## **Funding**

This research received no external funding.

## **Ethical Approval**

The study was approved by the ethical review committee of the Department of Ophthalmology, District Headquarter Hospital, Sheikhupura, Pakistan (DHQ-ED-22-145).

#### **Conflict of Interest**

None to declare.

#### References

 Alemayehu AM, Yibekal BT, Fekadu SA. Prevalence of vernal keratoconjunctivitis and its associated factors among children in Gambella town, southwest Ethiopia, June 2018.

- *PLoS One.* 2019;14(4):e0215528. https://doi.org/10.1371/journal.pone.0 215528
- Saboo US, Jain M, Reddy JC, Sangwan VS. Demographic and clinical profile of vernal keratoconjunctivitis at a tertiary eye care center in India. *Indian J Ophthalmol*. 2013;61(9):486-489. <a href="https://doi.org/10.4103/0301-4738.119431">https://doi.org/10.4103/0301-4738.119431</a>
- Akinsola F, Sonuga A, Aribaba O, Onakoya A, Adefule-Ositelu A. Vernal keratoconjunctivitis at Guinness Eye Centre, Luth (a five year study). Nig Q J Hosp Med. 2008;18(1):1-4. <a href="https://doi.org/10.4314/nqjhm.v18i1.4">https://doi.org/10.4314/nqjhm.v18i1.4</a> 4945
- Kumar S. Vernal keratoconjunctivitis: a major review. *Acta Ophthalmol*. 2009;87(2):133-147. <a href="https://doi.org/10.1111/j.1755-3768.2008.01347.x">https://doi.org/10.1111/j.1755-3768.2008.01347.x</a>
- 5. Duke RE, Odey F, De Smedt S. Vernal keratoconjunctivitis in public primary school children in Nigeria: prevalence and nomenclature. *Epidemiol Res Int.* 2016;2016:1-6.

## http://dx.doi.org/10.1155/2016/9854062

- Zicari A, Capata G, Nebbioso M, et al. Vernal Keratoconjunctivitis: an update focused on clinical grading system. *Ital J Pediatr*. 2019;45(1):1-6. <a href="https://doi.org/10.1186/s13052-019-0656-4">https://doi.org/10.1186/s13052-019-0656-4</a>
- 7. Hayilu D, Legesse K, Lakachew N, Asferaw M. Prevalence and associated factors of vernal keratoconjunctivitis among children in Gondar city, Northwest Ethiopia. *BMC Ophthalmol*. 2016;16(1):1-6.

- Chenge B, Makumyamviri A, Kaimbo W, Kaimbo D. Tropical endemic limbo-conjunctivitis in Lúbumbashi, Democratic Republic of the Congo. Bull Soc Belge Ophtalmol. 2003;(290):9-16.
- 9. Khan M, Kundi N, Saeed N. A Study of 530 cases of vernal conjunctivitis form the North Western Frontier Province of Pakistan. *Pak J Opthalmol.* 1986;(2):111-114.
- 10. Resnikoff S, Cornand G, Filliard G, Hugard L. Limbal vernal conjunctivitis in the tropics. *Rev Int Trachome*. 1988;65(3-4):21-72.
- 11. Shaikh A, Ovais S. The morbidity of vernal keratoconjunctivitis. *Pak J Ophthalmol*. 2001;3(17):86-89.
- 12. Leonardi A, Busca F, Motterle L, et al. Case series of 406 vernal keratoconiunctivitis patients: demographic and epidemiological study. Acta Ophthalmol Scand. 2006;84(3):406-410. https://doi.org/10.1111/j.1600-0420.2005.00622.x
- Lambiase A, Minchiotti S, Leonardi A, et al. Prospective, multicenter demographic and epidemiological study on vernal keratoconjunctivitis: a glimpse of ocular surface in Italian population. *Ophthalmic Epidemiol*. 2009;16(1):38-41. <a href="https://doi.org/10.1080/092865808025">https://doi.org/10.1080/092865808025</a>
   73177
- 14. Tabbara KF. Ocular complications of vernal keratoconjunctivitis. *Can J Ophthalmol*. 1999;34(2):88-92.
- 15. Ukponmwan CU. Vernal keratoconjunctivitis in Nigerians: 109 consecutive cases. *Trop Doc.* 2003;33(4):242-245.

- https://doi.org/10.1177/004947550303 300419
- 16. Kawuma M. The clinical picture of vernal kerato-conjunctivitis in Uganda. *Community Eye Health*. 2001;14(40):66-67.
- 17. Bonini S, Bonini S, Lambiase A, et al. Vernal keratoconjunctivitis revisited: a case series of 195 patients with long-term follow-up. *Ophthalmol*. 2000;107(6):1157-1163. <a href="https://doi.org/10.1016/S0161-6420(00)00092-0">https://doi.org/10.1016/S0161-6420(00)00092-0</a>
- Thera J, Hughes D, Tinley C, Bamani S, Traore L, Traoré J. Magnitude of vernal kerato conjunctivitis among school children in Koulikoro. *Sch J Appl Med Sci.* 2016;4(1):180-182.
- Ashwini K, Dhatri K, Rajeev K. Vernal keratoconjunctivitis in school children in north Bangalore: an epidemiological and clinical evaluation. J Evol Med Dent Sci. 2015;4(86):15070-15077.
- 20. Rajasekar K. A clinical study on aetiopathogenesis, course and presentation of vernal keratoconjunctivitis seeking tertiary eye care in Chennai. *J Evid Based Med Healthc*. 2018;5(31):2264-2267.
- Radhika R, Pushpa Latha M. Demographic and Clinical Profile of Vernal Keratoconjunctivitis in Teaching Hospital, Kurnool. *Int J Intg*

- *Med Sci.* 2021;8(2):976-80. https://dx.doi.org/10.16965/ijims.2021 .106
- Totan Y, Hepşen IbF, Çekiç O, Gündüz A, Aydın E. Incidence of keratoconus in subjects with vernal keratoconjunctivitis::

   a videokeratographic
   btudy.
   Ophthalmol.
   2001;108(4):824-827.
   https://doi.org/10.1016/S0161-6420(00)00664-3
- 23. Yan L, Jiang D, He J, Wong D, Lian Q. Limbal stem cells and corneal epithelial regeneration: current status and prospectives. *J Ocular Biol*. 2014;2(1):1-10.
- 24. Leonardi A. Vernal keratoconjunctivitis: pathogenesis and treatment. *Prog Retin Eye Res*. 2002;21(3):319-339. https://doi.org/10.1016/S1350-9462(02)00006-X
- Al-Akily SA, Bamashmus MA. Ocular complications of severe vernal keratoconjunctivitis (VKC) in Yemen. Saudi J Ophthalmol. 2011;25(3):291-294.
   <a href="https://doi.org/10.1016/j.sjopt.2011.02">https://doi.org/10.1016/j.sjopt.2011.02</a>
   .001
- 26. De Smedt S, Wildner G, Kestelyn P. Vernal keratoconjunctivitis: an update. *Br J Ophthalmol*. 2013;97(1):9-14. <a href="http://dx.doi.org/10.1136/bjophthalmol-2011-301376">http://dx.doi.org/10.1136/bjophthalmol-2011-301376</a>