Demographic and clinical variations of keratoconus in Saudi population

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Abstract:
PURPOSE: The aim of this prospective study was to identify the demographic and clinical variations of keratoconus (KC) in Saudi Arabia.

METHODS: A self-administered survey was completed by patients in Saudi hospitals. The survey included questions on demographics, educational level, treatment options, dry eye, eye rubbing because of allergy, residence, family history, and consanguineous marriage.

RESULTS: Six hundred and forty-eight patients (375 – male, 273 – female; mean age: 26.89 [standard deviation: 7.04] years; range: 11–50 years) were conducted at 13 central hospitals in all 13 administrative areas of Saudi Arabia over a 1-year period. Five hundred and forty-three (83.8%) patients had a secondary school diploma or diploma’s degree of education and mostly were from the Aseer and Riyadh regions. The geographical distribution rate of KC was highest in the mountainous areas. For dry eye, 21.9% and 44.8% of the patients, respectively, reported frequent or occasional dryness and 13.4% and 48.9% of the patients, respectively, reported frequent or occasional bouts of eye allergy. Furthermore, 17.9% and 61.9% of the patients, respectively, reported that they constantly or sometimes rubbed their eyes. Marriages were endogamous in 53.5% of the patients and the family history was positive by 56.8%. There was a history of ocular disease in 27% of the patients and the systemic disease was 13%.

CONCLUSION: This study is the first to describe the regional demographic and clinical variations of KC in Saudi Arabia. Its findings suggest that the different distribution of keratoconic patients between provinces is attributable to genetic and/or environmental factors.

Keywords: Demography, geography, keratoconus

Introduction

Keratoconus (KC) is a progressive, non-inflammatory degenerative disease of the cornea in which the central portion of the cornea becomes thinner and protrudes forward, causing myopia, irregular astigmatism, and finally visual impairment.[1,2] Classically, this disorder has its onset in puberty and is progressive until the third to fourth decade of life, at which time it is usually arrested.[2] Although the previous epidemiologic studies of KC vary widely in their findings as a result of the various diagnostic criteria and tools used, the frequency of the disease is most commonly reported to be 1 per 2000 per year and the prevalence to be 54.5 per 100,000.[2]

The genetic and environmental contributions to the etiology of KC remain unclear.[3] Reports reinforcing genetic factors have identified familial aggregation,[4,5] a higher concordance of ectasia in monozygotic twins than in dizygotic twins,[6] genetic identification of several loci,[5,7] an association with genetic systemic disorders,[8] and parental consanguinity.[9,10] An environmental factor, such as atopy, eye rubbing, or exposure to ultraviolet radiation, combined with a genetic predisposition has been reported to affect the development and severity of KC by eliciting...
a cascade of biochemical events in the cornea that results in KC.\textsuperscript{[4,8,11]}

Several studies have reported a marked difference in the prevalence of KC according to geographic location. In general, countries with sunny and warm climates, such as the Middle East and India, have a higher prevalence of KC than cooler and less sunny countries, such as the northern US, northern Europe, and Russia.\textsuperscript{[12-17]} Ultraviolet radiation increases with altitude by approximately 10% for every 1000 m of elevation.\textsuperscript{[18]} so individuals living in high mountainous areas are likely to have greater exposure to ultraviolet radiation.\textsuperscript{[12]}

There have been several studies of the characteristics and risk factors associated with KC worldwide.\textsuperscript{[9,10,19-25]} However, in Saudi Arabia, the terrain and climate vary from province to province, so few studies have investigated the regional incidence and prevalence of KC. The Taif city and Aseer regions have almost the same geographic characteristics and demographic variations.\textsuperscript{[12,26,27]} A case study of KC and its associated risk factors has not been carried out in the whole Saudi population, which is known to have a high incidence of the disease and a severe presentation at an early age in a specific region. The aim of this study was to investigate the demographic variations, geographic characteristics, and clinical features of KC in different areas of Saudi Arabia.

**Methods**

A prospective study was performed using a self-administered questionnaire that was handed to patients by optometrists at 13 public hospitals around Saudi Arabia for a 3-month period of time in each region from January 1, 2016, to the end of December 2016. The questionnaire was designed to obtain information on demographics (age, sex, place of birth, current residence, and education level) and potential risk factors for KC (including general state of health, family history of KC, associated systemic and ocular diseases, dryness, allergies, and eye rubbing). Other characteristics, such as blood type, blood group (Rh), treatment modalities used for KC, and family history of consanguineous marriage, were also included.

The questionnaire was prepared by a focus group comprising three experienced optometrists and was drafted in Arabic, which is the official language of Saudi Arabia. The questionnaire was sent to all optometrists working in public hospitals that have departments that provide ophthalmic services around Saudi Arabia. However, only 13 hospitals were responded to participate in this study.

Patients with KC were recruited to participate in the study at the time of their routine follow-up visit to an optometry or ophthalmology clinic. The study followed the tenets of the Declaration of Helsinki and was approved by the research ethics committee at the College of Applied Medical Sciences, King Saud University, Riyadh. The details of the study were explained to the patients, and a signed consent form was obtained from all study participants. The questionnaire was completed with the help of the attending optometrist if necessary.

The diagnosis of KC was made by an optometrist or ophthalmologist based on at least one of the frank clinical signs of KC, i.e., uncorrected myopic astigmatism with glasses, scissor motion, irregular or distorted mires in the early stages, stromal thinning, conical protrusion, Munson’s sign, Fleischer’s ring, Vogt’s striae, and moderate to advanced apical stromal scarring. Suspected cases for which the diagnosis of KC could not establish with confidence were excluded from the study. Furthermore, patients who declined to participate were excluded. All data were input into the computer using SPSS for Windows (version 21, IBM Corp., Armonk, NY, USA) for analysis. Descriptive statistics and analytical methods were used to describe the data collected from all KC demographic and educational level variables. Multiple response analysis was used to describe ocular history (allergy, dryness, and eye rubbing), since the patient may have one or more of the symptoms. Microsoft Excel 2010 (Redwood, MA, USA) was used to describe the frequency of keratoconic patients with ocular and systemic diseases.

**Results**

Six hundred and forty-eight patients with KC were enrolled in the study. The demographic data (age, sex, and educational level) for the study are shown in Table 1. The mean age of the KC patients at the time of the survey was 26.89 ± 7.04 (range, 11–50) years; the majority (88%) were aged 11–35 years, and the self-reported mean age at the time of diagnosis was 21.2 ± 6.4 (range, 6–49) years.

The proportions of patients were in male more than female by 57.9% and 42.1% respectively. The educational level of this study is shown in Table 1. Eighty-five percent of the patients had a secondary school or higher.

Table 2 shows where the data were collected and the birthplaces for the KC patients in each province. The Aseer and Riyadh...
regions contributed the greatest number of patients in the study (35.6% and 18.8%, respectively). However, in terms of population density, the mountainous regions of Al Baha, Aseer, and Najran had the highest rate of KC (0.0128%) followed by the desert region (0.0028%), and the coastal regions had the lowest rate (0.0014%), as shown in Table 3.

Of the 1207 eyes (1118 binocular, 89 monocular), 494 eyes were corrected by glasses, 363 by hard contact lens, 121 by soft contact lens, 73 eyes by cross-linking, 95 by penetrating keratoplasty, and 61 eyes by corneal rings [Figure 1].

Regarding ocular history, eye dryness was rated as constant in 142 (21.9%), occasional in 290 (44.8%), and rare in 216 (33.3%) KC patients. Eye allergy was reported to be constant by 87 (13.4%), occasional by 317 (48.9%), and rare by 244 (37.7%) KC patients. Eye rubbing was described as constant by 116 (17.9%), occasional by 401 (61.9%), and rare in 131 (20.2%) patients, as shown in Figure 2.

There were 347 (53.5%) reports of parents being cousins among patients’ families as well as 368 (56.8%) reports of a family history of KC in a parent, sibling, child, aunt, or uncle. Hundred seventy-four (27%) patients had ocular disease and another 87 (13%) patients had systemic disease.

The most common blood type was O in this study (62.2%), followed by A (25.5%). The proportion of patients who were Rh (+) was (88.2%) whereas Rh (−) was (11.8%).

**Discussion**

The ability to describe the distribution rate of a disease is important for predicting current and future clinical needs and for establishing the characteristics of that disease in a specific population in different geographical locations. This study was performed in collaboration with optometrists in 13 hospitals across Saudi Arabia in order to evaluate the characteristics of KC and its rate distribution in the different regions of the country.

Table 1 presents the demographic data for age, sex, and education level of participants in this study. Recent investigations of KC in the Middle Eastern population have reported mean ages at the time of study in the range of 25–27.6 years.[10,27,28] The mean age of the patients with KC at the time of survey in the present study was 26.89 ± 7.04 years, with a majority (88.0%, n = 570) being aged 11–35 years. Further studies have reported a mean age at the time of diagnosis in the range of 18.5–22.5 years and suggested an early age of onset in Middle East populations.[12,19‑22,29] In our study, the self-reported estimated mean age at the time of diagnosis was 21.2 ± 6.4 years, with 88.7% being younger than 30 years.

In this study, male participants outnumbered female participants, which is consistent with several previous reports.[10,30,31] This study revealed that approximately 85% of the patients had a secondary school or higher shown in Table 1, believing that this may be because of the free education and compulsory for students of general education. This finding is consistent with the Collaborative Longitudinal Evaluation of KC study.[32]

The epidemiology of many diseases varies widely from one part of the world to another as a result of variation in geographic, demographic, racial, climatic, and environmental

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**Table 2: Place of data collection and place of birth for keratoconus patients**

| City            | Place of data collection, n (%) | Place of birth, n (%) |
|-----------------|---------------------------------|-----------------------|
| Mountainous regions |                                 |                       |
| Al Baha         | 52 (8.0)                        | 51 (7.9)              |
| Aseer           | 231 (35.6)                      | 213 (32.9)            |
| Najran          | 25 (3.9)                        | 42 (6.5)              |
| Desert regions  |                                 |                       |
| Riyadh          | 122 (18.8)                      | 79 (12.2)             |
| Gassim          | 22 (3.4)                        | 31 (4.8)              |
| Al Jouf         | 14 (2.2)                        | 14 (2.2)              |
| Hail            | 18 (2.8)                        | 21 (3.2)              |
| Northern border | 12 (1.9)                        | 13 (2.0)              |
| Coastal regions |                                 |                       |
| Eastern province| 49 (7.6)                        | 55 (8.5)              |
| Makkah          | 60 (9.3)                        | 58 (9.0)              |
| Madinah         | 12 (1.9)                        | 14 (2.2)              |
| Tabuk           | 15 (2.3)                        | 13 (2.0)              |
| Jazan           | 16 (2.8)                        | 28 (4.3)              |
| Other           | -                               | 16 (2.5)              |
| Total           | 648 (100)                       | 648 (100)             |
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**Table 3: Distribution rate in each geographical area across Saudi Arabia**

| Geographical area | Population density age range (11-50) | Number of patients | Distribution rate (%) |
|-------------------|--------------------------------------|-------------------|-----------------------|
| Mountainous regions | 1,871,394 | 308 | 0.01646 |
| Desert regions | 5,131,414 | 188 | 0.0037 |
| Coastal regions | 8,137,336 | 152 | 0.00187 |

characteristics. Saudi Arabia is a country that contains mountainous, desert, and coastal regions. Therefore, the survey was undertaken in the main hospitals for a 3-month period of time in each region to ensure consistency of the data collected.

According to the General Authority for Statistics, the mountainous regions are less densely populated than the desert and coastal regions.[33] Therefore, the highest rate of KC patients was in the mountainous regions (0.0122%) followed by the desert region (0.0028%). The coastal and semi-coastal regions had the lowest distribution rate of the disease [0.0014%; Table 3]. However, the higher rate of KC patients in Riyadh, Makkah, and the eastern regions was expected because of the high population density in these areas and the influx of patients from other areas seeking more advanced health care.[34]

_Eyeglasses were the most common treatment modality (40.9%) followed by hard and soft contact lenses (30.1 and 10.0%, respectively). The least commonly used treatment was surgery (penetrating keratoplasty in 7.9%, corneal rings in 6.0%, and cross-linking in 5.1%). This treatment pattern may reflect the preference for optical treatment in the mild and moderate stages of the disease and lack of availability of surgical services in some regions._

Environmental or geographic factors might contribute to the high rate of KC patients in the mountainous regions of Al Baha, Aseer, and Najran, which have similar geographic topography. Individuals living at these high altitudes are likely to be more prone to oxidative corneal damage because of exposure to high levels of ultraviolet radiation,[35] given that ultraviolet radiation increases with altitude by approximately 10% for every 1000 m of elevation.[18]

Other potential contributors to the development of the disease are the lower oxygen pressure and exchange of atmospheric gasses at high altitudes, as would be the case in Aseer province.[12] The physiological changes in the cornea that occur under hypoxic conditions could trigger a change in glycogen metabolism whereby anaerobic metabolism provides less energy than aerobic metabolism, leading to lower glycogen stores in the epithelium.[36]

Twenty-seven percent of the KC patients experienced some common ocular diseases such as cataract and glaucoma. Small cases (13%) of patients report systemic diseases such as diabetes and hypertension, which is comparable to a previous study.[32-37] However, none of the patients report the serious systemic diseases (e.g., connective tissue disorders) that have been associated with KC.

Patients with atopy are more likely to develop KC as a result of eye rubbing because of a predisposition to the disease.[38] The risk of KC may be affected by environmental or geographic factors, such as a sunny, dusty, and warm climate, which could trigger eye dryness and allergy.[14] Therefore, the interaction between allergy and eye rubbing could cause rapid progression of KC.[39] The results shown in Figure 2 indicate a direct relationship between environmental or geographical factors and KC disease and support previous reports of a direct relationship between KC and eye dryness, allergy, and eye rubbing.[12,14]

A genetic factor possibly underlying the higher incidence of KC in Asian populations living in Britain than in their white counterparts despite similar environmental influences is the high rate of consanguineous marriages, especially first-cousin unions, in Asian populations that originate from Indian, Pakistani, and Bangladesh.[19-21] We found a slightly higher rate of KC in patients who were the product of a consanguineous marriage than in those who were not. The endogamy rate was in the study (53.5%) indicating that consanguinity is a possible predictor of KC. Moreover, a greater proportion of patients reported having one or more family members with KC (56.8%), which indicates a direct relationship between KC and family history.

Blood group O and the Rh (+) phenotype were most common, followed by blood group A and the Rh (−) phenotype, which is in line with a previous report indicating that there is no significant excess of any particular blood group in patients with KC.[40]

This study has several limitations related to the method used to collect the study data, which was based on verbal reporting rather than objective assessment, especially the questions related to risk factors for KC, such as family history of the disease, consanguinity, dryness, allergies, and eye rubbing. Even though invitations directed to 18 hospitals, but only 13 hospitals were participated in this study which are mostly covered all the regions of Saudi Arabia. Another limitation was the unavailability of a tool that can measure ultraviolet exposure in different geographic locations. Further research focusing on the interaction between ultraviolet exposure and development of KC is needed to confirm and better interpret our results.

**Conclusion**

This study found a wide variation in the distribution rate of KC across regions of Saudi Arabia. KC was most common in the mountainous regions of Al Baha, Aseer, and Najran. Consanguinity, a family history of KC, eye rubbing, dryness, and allergy increased the risk of developing KC. Our data suggest an interaction between genetic and environmental...
factors in individuals who develop KC. The data from this study will aid the “Saudi Ministry of Health” to provide adequate eye care services for KC patients throughout Saudi Arabia.

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Conflicts of interest
There are no conflicts of interest.

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