Prevalence of keratoconus in refractive surgery practice population in North Macedonia

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Abstract
Purpose To determine the prevalence of keratoconus (KC) in relation to ethnicity in a group of people who consulted an ophthalmological care institution seeking for refractive surgery in N. Macedonia.

Methods This was a cross-sectional, interventional retrospective study. Chart reviews were performed for all new patients attending between January 2016 and January 2020 at the Sistina Ophthalmology Hospital in Skopje. All patients were screened; KC diagnosis and classification were based on the corneal topography. Ethnicity and gender classifications were according to patients’ self-opinions.

Results A total of 2812 patients charts reviewed. The mean age was 31.71 years (SD ±9.73), and 1209 (43%) were male. A total of 2050 (72.9%) declared themselves as Macedonians, 649 (23.1%) Albanians, 76 (2.7%) Turks and 37 (1.3%) in other ethnicities. Differences in age between the ethnic groups were statistically significant ($\chi^2 = 90.225$, $p < 0.001$). KC was diagnosed in 343 patients (12.2%), while 9 (0.7%) were KC suspects and 6 (0.21%) presented pellucid marginal degeneration. KC was more frequent in males ($n = 246$, 71.7% of total) and skewed toward younger patients. Increasing patients’ age decreased the odds of KC diagnosis by 3.7% (95% CI 1.8%-4.4%) per annum. Males were four times more likely to be diagnosed with KC (AOR = 4.01; 95% CI 3.12–5.16). In comparison with Macedonian patients, Turks were more likely to be diagnosed with KC (AOR = 4.09; 95% CI 2.47–6.78). There was no difference between Macedonians and Albanians ($p = 0.08$).

Conclusion The prevalence of KC at a refractive surgery practice in N. Macedonia is much higher
compared with general population (6.8/100,000) and similar to the prevalence in Middle East Asia. Nationwide screening programs are needed to diagnose the disease earlier.

**Keywords** Keratoconus · Epidemiology · Prevalence

**Introduction**

Keratoconus (KC) is a disorder characterized by a conical protrusion and thinning of the cornea. Corneal scars impacting on the overall quality of vision are often associated with KC. Individuals with incipient KC may be asymptomatic with normally appearing corneas except for changes in astigmatism. The apex of the cone is frequently displaced inferiorly and results in irregular astigmatism. In the advanced stage of the disease, the irregular astigmatism can be neither corrected with glasses nor contact lenses and progresses to marked visual impairment [1, 2]. The etiology of keratoconus is not fully understood, but is thought to be multifactorial with the possible participation of pro-inflammatory factors in its development and progression. Both genetic and external risk factors linked to KC have been identified, and these are summarized in Table 1. A positive family history is often associated with KC but it is also viewed as a sporadic disease that is strongly associated with systemic collagen tissue disorders and some syndromes [3–7].

Inflammatory mediators found in the tear film raised a key question concerning the definition of KC: Is it a noninflammatory or an inflammatory disease? [1, 5, 6] According to McMonnies, the inflammation is a result of eye rubbing [5]. Chronic mechanical trauma of the cornea caused by less than ideal contact lenses can lead to release of matrix metalloproteinases and inflammatory mediators which lead to corneal weakening. Other predisposing factors (such as allergy, chronic dryness or even air pollution) irritate the eyes and promote inflammation leading to rubbing, and these act as precursors to corneal ectasia [6, 7].

The prevalence of KC varies between geographical regions and ethnic groups [8]. Some of the differences in the reported incidence of KC are profound. For example, a study on a Russian population reported an incidence of 0.3 cases per 100,000 people, while a study on a central Indian population reported an incidence of 2300 cases per 100,000 people [8, 9]. KC is far more frequent in Asian, Polynesian and Middle Eastern populations than in Caucasians and is more frequent in geographical areas with plenty of sunshine and hot weather compared with regions with less sunshine and cooler weather [10, 11]. Furthermore, endogamy has also been cited as a potential risk factor in some populations [2, 12, 13]. A Dutch nationwide study from 2016 disclosed surprising results and compels us to rethink KC by removing it from the rare disease category [14]. The estimated prevalence of KC in the general population was just under 1:377 (265 cases per 100,000, 95% confidence interval).

| Table 1 Clinical phenotypes for keratoconus |
|---------------------------------------------|
| **Familial**                              | Autosomal dominant inheritance |
| **Genetic diseases and syndromes**         | Sporadic                      |
| Down’s syndrome                           | Osteogenesis imperfecta       |
| Marfan’s syndrome                         | Oculudentodigital syndrome    |
| Apert syndrome                            |                                |
| **Inflammatory diseases**                 | Atopy                         |
| Allergic inflammation of the eye          | Suboptimal contact lenses     |
| Dry eye                                   | Eye compression habits during sleep |
| **Mechanical trauma**                     | Eye rubbing                   |

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Values that are fivefold to tenfold higher than previously reported in relatively large population studies [13]. The more recent studies tend to report higher prevalence rates for KC. For example, in 1959 a study based in USA reported a prevalence rate of 0.12% and a 2018 investigation in Iran reported a prevalence rate of 3.3% [15, 16]. The detection of any condition is ultimately reliant upon the procedures and criteria employed for the detection. Earlier studies depended upon less refined, more subjective, instruments for detecting KC. In contrast, recent investigators employed more sophisticated, objective, screening systems for KC detection. Another example of a higher prevalence rate in a modern setting is the result from a study conducted on Maori high school children based in New Zealand where the rate was 2.22% [17]. Environmental factors (e.g., air pollution), rises in the incidence of allergies and atopic conditions, changes linked to KC, coupled with technological advances for early detection of KC, are expected to yield larger values for the prevalence of KC. There is a paucity of epidemiological data on KC from N. Macedonia and its surround. Refractive surgery departments attract patients with many types of visual impairment, all seeking a solution for their reduced vision. Individuals might not be aware that they have visual symptoms resulting from undiagnosed KC. Thus, the prevalence of KC, and subclinical KC, among patients seeking refractive surgery is much higher than in the general population ranging from 3.9 to 18.7% [18–25]. Refractive surgery clinics are well-placed frontline centers for detecting KC because of the extensive preoperative screening examinations that are provided as part of the routine service.

Data on the prevalence of KC in N. Macedonia are limited. A preliminary investigation revealed just one contemporary study, by Ljubic published in 2009, where the patients were classified as KC based on keratometry values obtained during contact lens fitting [26].

The aim of our study was to determine the prevalence of KC among the self-selected population seeking refractive surgery at the Sistina Ophthalmology Hospital in Skopje, N. Macedonia, and to determine whether factors such as age, gender and ethnicity were significantly associated with KC.

**Materials and methods**

A survey consisting of a retrospective chart review was performed on all new patient cases that attended over the period between January 2016 and January 2020. Charts of patients with a previous history of corneal surgery, corneal opacity and those previously examined by clinicians of Sistina Ophthalmology Hospital prior to January 2016 were excluded. A total of 2812 self-selected patients underwent KC screening as part of the preoperative evaluation for refractive surgery during this period.

The investigation was approved by the Ethics Committee at Sistina Ophthalmology Hospital in Skopje. The Tenets of the Helsinki Agreement were followed throughout.

All patients underwent a full comprehensive screening which consisted of manifest and cycloplegic monocular refraction, slit lamp examination, dilated fundus examination, intraocular pressure measurement (Icare™, Revenio Group Corp, Finland), tear film quantity and stability assessment (Schirmer test, Tear Break Time Test) and Pentacam HR (Oculus Optikgeräte GmbH, Wetzlar, Germany). Prior to the examination, all patients were advised to cease wearing any soft contact lenses for no less than 7 days and 21 days for rigid gas-permeable contact lenses.

The classification of the patients was based on a modification of systems based on the corneal tomographic parameters [23, 27]. Our subjects were classified as having KC if at least two of the following criteria were met:

1. Corneal thickness < 470 µm,
2. Difference in corneal thickness between the corneal apex and the thinnest region > 10 µm
3. Corneal steepening > 48D,
4. Skewed radial axis > 22°,
5. Posterior surface elevation > 15 µm,
6. Inferior-superior (I-S) asymmetry > 1.4D.

Subjects were classified as KC suspects if one of the following criteria was met:

1. Corneal thickness < 450 µm,
2. Asymmetric bowtie pattern on corneal topography map,
3. Corneal steepening ≥ 48D.
4. Posterior surface elevation $> 25 \, \mu m$,
5. I-S asymmetry $> 1.6$D

Subjects were classified as pellucid marginal degeneration (PMD) if at least two of the following criteria were met:

1. Peripheral ectasia
2. Claw pattern on the anterior surface curvature map
3. Inferior peripheral thinning
4. 'Kissing birds' pattern on elevation maps
5. Bell sign on thickness map
6. Largely displaced thinnest region

If one eye was classified as KC, the patient was placed into the KC group; if the worst eye was classified as a KC suspect, then the patient was placed into the KC suspect group; and if one eye was classified as PMD, the patient was placed in PMD group.

Treatment of data

The data were entered into an Excel spreadsheet (Microsoft, Redmond, WA), and each patient was classified into one of three categories: KC, KC suspect, or PMD. Data in each classification were further stratified according to age (into groups: $\leq 20$, $21–30$, $31–40$ and $> 40$ years of age), gender (male and female) and ethnicity (Macedonian, Albanian, Turkish or other) and analyzed using SPSS.26 statistical software. The normality of the data was checked using Kolmogorov–Smirnov test. The ages were compared in relation to patient ethnicity (Kruskal–Wallis $H$ test). The average age of different genders was compared in each category (Mann–Whitney $U$ test). Furthermore, the prediction of the occurrence of the diagnose of KC was analyzed using binomial logistic regression. Gender and ethnicity were used as a categorical covariate and age as a continuous covariate. The adjusted odds ratios (AOR) and 95% confidence interval (95% CI) values were also calculated.

Results

During the 4-year period at Sistina Ophthalmology Hospital in Skopje, 2812 patients seeking a better solution of their refractive problem were analyzed. None fulfilled the exclusion criteria or presented with poor unreliable Pentacam images. Among the participants in the study, the age ranged from 10 to 76 years; average was 31.7 years ($\pm 9.73$). A total of 1209 (43%) patients were male and 1603 (57%) were females. On average, males were 32.1 ($\pm 10.08$) and females 31.4 ($\pm 9.44$) years old, and the difference between the groups was not statistically significant ($U=938,772, \ p=0.156$). The chief results are shown in Tables 2, 3 and 4.

Three hundred and forty-three patients, or 12.2% (95% CI 11.1–13.5) of the total examined, were classified as KC and 9 as KC suspects. The suspects were excluded from the calculation of KC prevalence. Another six patients were diagnosed PMD and, since it is a different disease in the family of primary ectasies, were also excluded from the calculation of KC. Fourteen cases were classified as unilateral KC. KC was more frequent in males ($n=246$, 71.7% of total) than in females ($n=97$, 28.3% of total) and more frequently diagnosed among the younger patients.

| Ethnicities | Total |
|-------------|-------|
|             | Number of females (%) | 1203 (58.7%) | 354 (54.5%) | 30 (39.5%) | 16 (43.2%) | 1603 (57.0%) |
|             | Mean age (SD) | 32.42 ($\pm 9.54$) | 28.27 ($\pm 8.41$) | 27.90 ($\pm 8.56$) | 35.25 ($\pm 8.38$) | 31.44 ($\pm 9.44$) |
|             | Number of males (%) | 847 (41.3%) | 295 (45.5%) | 46 (60.5%) | 21 (56.8%) | 1209 (43.0%) |
|             | Mean age (SD) | 32.86 ($\pm 10.16$) | 30.17 ($\pm 9.51$) | 28.28 ($\pm 9.02$) | 34.62 ($\pm 11.85$) | 32.06 ($\pm 10.08$) |
|             | Total (%) | 2050 (100.0%) | 649 (100.0%) | 76 (100.0%) | 37 (100.0%) | 2812 (100.0%) |
|             | Mean age (SD) | 32.60 ($\pm 9.80$) | 29.13 ($\pm 8.97$) | 28.13 ($\pm 8.79$) | 34.89 ($\pm 10.36$) | 31.71 ($\pm 9.73$) |

Ethnicities in the sample population are stratified by age and gender and presented in total number of patients and percent (%).
The prevalence of KC in each age group (≤ 20, 21–30, 31–40 and > 40 years) was 18.1%, 41.7%, 27.4% and 12.8%.

The data were subjected to binomial logistic regression analysis (the Hosmer–Lemeshow test) to determine the significance of age, gender and ethnicity on the likelihood of a diagnosis of KC among the patients checked in the Hospital. The variance in the model (Nagelkerke, $r^2$) was 12.8% and accurately classified 87.7% of cases.

The results show that patient age significantly affected the likelihood of KC diagnosis ($p < 0.05$). Increasing patient age decreased the odds of the diagnosis by 3.7% (95% CI 4.4–1.8%) per annum.

Regarding patient gender, results show that males were 4× more likely to be diagnosed with KC compared with females (AOR = 4.01; 95% CI 3.12–5.16) even though there were more females ($n = 1603$) than males ($n = 1209$) in the initial cohort.

In comparison with the main reference group (Macedonian patients), Turks had the highest odds to be diagnosed with KC (AOR = 4.09; 95% CI 2.47–6.78). Furthermore, in comparison with the same reference group, the odds for patients of other ethnicities to have been diagnosed with KC was 2.37 (AOR = 2.37; 95% CI 1.06–5.30). On the other hand, Albanian patients did not show a statistically significant difference ($p = 0.084$). Results indicate that it is almost equally possible for an Albanian patient to be diagnosed with KC when compared with a Macedonian.

### Discussion

There is a lack of fully comprehensive data on the worldwide prevalence of KC, and this has attracted interest in recent epidemiological studies. Clinic-based studies conducted in refractive surgery clinics tend to attract higher KC prevalence rates compared...
The prevalence rate revealed in this study, 12.2%, is low compared with Saudi Arabia (18.7% [23]), on par with rates in Serbia and Turkey (11.4% [25], 8.1–14.1% [19]), and high compared with USA (6.6% [18]) and Colombia (3.9% [21]).

The Sistina Ophthalmology Hospital was the first institution in N. Macedonia offering modern corneal tomography (Pentacam) and has the highest volume of refractive surgery in the territory. Thus, the data from this unit can be regarded as a reliable estimate for the prevalence KC in a refractive surgery department.

We are aware of only two other studies on refractive surgery populations in the territories around N. Macedonia [21, 24]. However, the design of these other studies did not consider ethnicity and the age ranges in the sample groups were limited.

There is no nationwide screening program for KC in N. Macedonia. The only figure for the prevalence of KC in N. Macedonian population is 6.8 per 100,000 for the general population [24]. But, this former study had the weakness of having estimated the prevalence assuming that half of all keratoconus cases of the country had been examined in a specific contact lens center, and therefore, it is not really possible to consider it as a prevalence based on a population study, nor applicable to the general population.

Nevertheless, the prevalence of 12.2% in the current study sample is much higher than the previous estimate reported in the former Ljubic study [24].

Several reason might explain the difference: Firstly, the estimation made by Ljubic, assuming that half of the keratoconus cases of the country attended a specific contact lens center, could have led to a gross underestimation of the real prevalence of the condition. Secondly, as seen in other studies, the subgroup of patients seeking refractive surgery show a high prevalence of keratoconus [18–23].

Geographically, Macedonia is sandwiched between Northern Europe and the Middle East. A sunny and dry climate is cited as one of the predisposing environmental factors for KC development, and this could be the reason why our results correspond more with those quoted for the Middle East than Europe [4]. Another reason may be the multi-ethnicity of the population in Macedonia resulting in greater genetic diversity. For the sake of comparison, we were unable to find any reliable figures on the prevalence of KC in regions such as Greece, Bulgaria and Albania.

Gender

There are uncertainties concerning gender as a predisposing factor in the diagnosis of KC in the different refractive surgery populations around the world. Studies by Omer [28] and Althomali et al. [24] found the prevalence in males and females was about the same, but Kozomara et al. [22] found slightly higher prevalence among males than females.

Our study found that males had a 4× greater chance of being diagnosed with KC than females, and the prevalence values of 71.7% for males and 28.3% for females are very similar to the results of a more recent study by Bejdic et al. [25].

The Valdez-Garcia study in Mexico found KC affected females twice as more frequently than males (66% vs. 33%) [29] The prevalence of KC in an adolescent population in Jerusalem was 5× more frequent in males, and contrary to this, a report from India claimed KC predominantly affected females [10, 30]. The exact age of onset remains unknown when KC is diagnosed. KC is often suspected when there is a major shift in astigmatism, or an unusual retinoscopic reflex is detected, or there is an increase in corneal and ocular higher-order aberrations, or uncertainties in subjective refraction occur. But to pinpoint when the changes that led to the detection of these phenomena commenced remains elusive. The time when diagnosis is made depends on many factors including the quality of the local healthcare system, the existence of nationwide screening and the willingness of patients to come forward.

The mean age in the cohort was 31.7 years, and the difference between the genders was not significant. Compared to other similar studies, our patients were older. This may be due to longer lag between the manifestation of symptoms and final diagnosis.

KC was most frequently diagnosed in the age group 21–30 years of age (41.35%), and a total of 59.8% were younger than 30 years at the time of diagnosis. Patients’ age significantly affects the likelihood of diagnosis, by lowering the odds of occurrence by 3.7% per year. This supports the previous findings that age is inversely correlated with the diagnosis of KC, the opposite of what is commonly associated with most chronic diseases [31,
However, this finding opposes the result from Wills Eye hospital in Philadelphia where, over a single year, 40% of KC diagnoses were for patients aged above 50 [33]. Refractive surgery units tend to attract a younger population seeking a solution for their visual impairment. Secondary and tertiary centers, like the Wills Eye hospital, attract a much broader spectrum of patients with other general and/or long-term ophthalmic health issues.

Ethnicity

Compared to Caucasians, the incidence of KC in Asians living in the UK is 4.4 to 9.2× higher in patients referred to secondary care [34–36]. Our study showed the occurrence of KC was 4.1× greater among the attending Turkish patients compared with the Macedonians. Data for the incidence, or prevalence, of KC in the Turkish population are scant. The prevalence of KC in our Turkish cases, 40.8%, is much higher than 8.1% and 14.1% values noted in a study reported in 2007 [19]. The number of cases of Turkish origin was 37 accounting for just 2.7% of the total, and these were significantly younger than the Macedonians. Consequently, we cannot rule out that the overall low number of Turkish cases did not skew the results. Turkish minorities have a tendency toward a high consanguinity rate of up to 90%, according to some sources, and this is associated with the accumulation of genetic factors linked to KC and other genetic conditions [37]. Hence, it is reasonable for this to contribute toward the higher odds for KC in some groups relative to others [30, 31]. An accumulation of genetic factors, coupled with the low number of cases of Turkish origin, may have contributed to the higher likelihood of detecting KC in these cases. The higher odds in the remaining groups cannot be reliably explained because the numbers were too low (<1.3% of the total). The similar odds for KC among Macedonians and Albanians were expected due to geographical and habitual proximity. The Albanian community in Macedonia is significantly larger than the Turkish and nurtures relationships with neighboring Kosovo and Albania itself. Furthermore, there is no evidence of different rates of consanguinity between Albanians and Macedonians.

Strengths and limitations of this study

The main limitation of this study revolves around sample size, especially for patients of Turkish ethnicity, and inevitably that can result in some bias. The study was performed in the refractive surgery unit of a private hospital that, in itself, leads to a selected group of individuals with refractive issues availing themselves for treatment.

In summary, there was a higher prevalence of keratoconus in N. Macedonia compared to other territories. But the prevalence was on par with values quoted for the Middle East, and this may be due to climatic similarities. The age when patients were diagnosed was higher than generally expected and should be further investigated. National keratoconus screening programs should be extended to include a broader spectrum of subjects.

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Declarations

Conflict of interest

The authors report no conflicts of interest concerning this study. The authors alone are responsible for the content and writing of the paper.

Ethical approval

The study was performed under the tenets of Helsinki agreement and approved by the Ethics committee at the Sistina Ophthalmology hospital.

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