Prevalence of Keratoconus in Refractive Surgery Practice Population in North Macedonia

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Research Article

Keywords: keratoconus, epidemiology, prevalence, refractive surgery

Posted Date: May 4th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-460380/v1>

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Abstract

Purpose: To determine the prevalence of keratoconus (KC) in relation to ethnicity 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 was 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), 1209 (43%) were male. 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 was statistically significant ($\chi^2=90.225$, $p<0.001$). KC was diagnosed in 343 patients (12.2%), 9 were KC suspects and 6 were pellucid marginal degeneration. KC was more frequent in males ($n=246$, 71.7% of total) and skewed towards younger patients. Increasing patients' age decreased the odds of KC diagnosis by 3.7%(95% CI:1.8%-4.4%) per annum. Males were 4 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 and similar to the prevalence in Middle East Asia. Nationwide screening programs are needed to diagnose the disease earlier.

Introduction:

Keratoconus (KC) is a disorder characterized by a conical protrusion and thinning of the cornea. 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 multifactorial and often viewed as a sporadic disease. KC is also strongly associated with systemic collagen tissue disorders and some syndromes [3]. Recent studies show that certain extrinsic factors may play key roles in the development of KC even in those without any genetic predisposition or collagen tissue disorders. Continuous mechanical trauma of the cornea, in the manner of eye rubbing, plays a major role in the etiology of the condition both in genetically predisposed individuals and those without any other constitutional risk factor [4]. Inflammatory mediators found in the tear film raised a key question concerning the definition of KC: Is it a non-inflammatory or an inflammatory disease [4, 5]? According to McMonnies, the inflammation is a result of eye rubbing[6]. Other predisposing factors (such as allergy, chronic dryness or even air pollution), irritate the eyes, promote inflammation leading to rubbing and these act as precursors to corneal ectasia [6].

The prevalence of KC varies between geographic regions and ethnic groups [7]. 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 2,300 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].

A Dutch nationwide study from 2016 disclosed surprising results and compels us to rethink KC by removing it from the rare disease category [12]. The estimated prevalence of KC in the general population was just under 1:377 (265 cases per 100,000, 95% CI: 260–270). Values that are 5 to 10-fold higher than previously reported in relatively large population studies [11]. Also, a study from New Zealand found that in a Maori population, the prevalence of KC among high school children was unusually high at 1:45 [13].

There is a paucity of epidemiological data on KC from N. Macedonia and its' surround.

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.

Refractive surgery departments attract patients with many types of visual impairment, all seeking a solution for their reduced vision. The patient might not be aware that s/he has visual symptoms resulting from undiagnosed KC. 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 is 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 [14].

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

Materials And Methods:

A retrospective chart review was performed on all new patient cases that attended over the period between January 2016 and January 2020. A total of 2812 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 [15, 16]. Our subjects were classified as having KC if at least two of the following criteria were met:

1. corneal thickness $< 470\mu\text{m}$,
2. difference in corneal thickness between the corneal apex and the thinnest region $> 10\mu\text{m}$
3. corneal steepening $> 48\text{D}$,
4. skewed radial axis $> 22^\circ$,
5. posterior surface elevation $> 15\mu\text{m}$,
6. Inferior-superior (I-S) asymmetry $> 1.4\text{D}$.

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

1. corneal thickness $< 450\mu\text{m}$,
2. asymmetric bowtie pattern on corneal topography map,
3. corneal steepening $\geq 48\text{D}$,
4. posterior surface elevation $> 25\mu\text{m}$,
5. I-S asymmetry $> 1.6\text{D}$

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 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: ≤ 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. Among the participants in the study, the age ranged from 10 to 76 years, average was 31.7 years (SD, ± 9.73). 1209 (43%) patients were male and 1603 (57%) were females. On average, males were 32.1 (SD, ± 10.08) and females 31.4 (SD, ± 9.44) years old, the difference between the groups was not statistically significant ($U = 938772$, $p = 0.156$). The chief results are shown in Tables 1–3.

Table 1
Ethnic groups, gender and age of sample population

	Ethnicities				
	Macedonian	Albanian	Turkish	Other	Total
Number of females (%)	1203 (58.7%)	354 (54.5%)	30 (39.5%)	16 (43.2%)	1603 (57.0%)
Mean age (SD)	32.42 (± 9.54)	28.27 (± 8.41)	27.90 (± 8.56)	35.25 (± 8.38)	31.44 (± 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 (± 10.16)	30.17 (± 9.51)	28.28 (± 9.02)	34.62 (± 11.85)	32.06 (± 10.08)
Total (%)	2050 (100.0%)	649 (100.0%)	76 (100.0%)	37 (100.0%)	2812 (100.0%)
Mean age (SD)	32.60 (± 9.80)	29.13 (± 8.97)	28.13 (± 8.79)	34.89 (± 10.36)	31.71 (± 9.73)

Ethnicities in the sample population are stratified by age and gender and presented in total number of patients and percent (%).

Table 2
Ethnic groups, gender and age of patients with keratoconus

Ethnicities					
	Macedonian	Albanian	Turkish	Other	Total
Number of female (%)	62	23	9	3	97
	(26,4%)	(33,8%)	(29,0%)	(33,3%)	(28,3%)
Mean age (SD)	30,29	29,26	27,67	35,33	29,96
	(± 11,41)	(± 9,49)	(± 9,27)	(± 7,64)	(± 10,65)
Number of male (%)	173	45	22	6	246
	(73,6%)	(66,2%)	(71,0%)	(66,7%)	(71,7%)
Mean age (SD)	30,09	27,53	26,91	29,83	29,33
	(± 9,58)	(± 8,26)	(± 9,47)	(± 13,88)	(± 9,48)
Total(%)	235	68	31	9	343
	(100,0%)	(100,0%)	(100,0%)	(100,0%)	(100,0%)
Mean age (SD)	30,14	28,12	27,13	31,67	29,51
	(± 10,07)	(± 8,67)	(± 9,27)	(± 11,94)	(± 9,81)

Ethnicities in the keratoconus group are stratified by age and gender and presented in total number and percent (%).

Table 3
Odds Ratio for the occurrence of the KC regarding the patient characteristics

	Sig. = p value (p < 0.05)	AOR	95% C.I for AOR
GENDER			
Female			
Male	.000	4.010	(3.116–5.160)
AGE (76-10years)	.000	.969	(0.956–0.982)
ETHNICITY			
Macedonian			
Albanian	.084	.770	(0.573–1.035)
Turks	.000	4.090	(2.467–6.779)
Other	.036	2.366	(1.057–5.298)
Constant	.000	.168	
*AOR = Adjusted odds ratios, * C.I. = Confidence interval			

In the gender category, the adjusted odds ratio (AOR) was calculated in males over the reference group of females. In the ethnicity categories, the AOR values for the Albanians, Turks and others were calculated over the reference group of Macedonians. 95% Confidence interval (CI) for AOR are noted in parentheses.

Decreasing patients' age increased the odds of diagnosing KC.

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 6 patients were diagnosed PMD and, since it is a different disease in the family of primary ecstasias, 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.

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 times 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. Studies conducted in refractive surgery clinics show higher KC prevalence values compared with nationwide studies [12, 16–18]. 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.

Our findings are similar to results observed in studies carried out in Iran, Iraq, Saudi Arabia, but not more geographically closer regions [7–11, 19, 20]. We are aware of only two other studies on refractive surgery populations in the region around N. Macedonia. The prevalence of KC in these studies was 2.9% and 8.5% respectively, values much lower compared with the current study [19, 20]. 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 [14]. This was based on a study performed between 1998 and 2004 where patients were classified based on clinical examination and keratometry values in patients considering contact lens wear [14].

The prevalence of 12.2% in our study sample is much higher than the previous estimate reported for the Ljubic study [14]. The main reason for the difference may be due to the diagnosis, which today can be made with more sophisticated objective devices on clinically asymptomatic patients with good visual acuity.

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 [17] and Talal et al[21] found the prevalence in males and females was about the same, but Kozomara et al[20] found slightly higher prevalence among males than females.

Our study found that males had a 4 times 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 [19].

The Valdez-Garcia study in Mexico found KC affected females twice as more frequently than males (66% vs. 33%)[22]. The prevalence of KC in an adolescent population in Jerusalem was 5 times more frequent in males, and contrary to this, a report from India claimed KC predominantly affected females [23, 24]. 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 diagnose, 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 [25, 26]. 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 [27]. 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 times higher in patients referred to secondary care [28–30].

Our study showed the occurrence of KC was 4.1 times greater among the attending Turkish patients compared with the Macedonians. Data for the incidence, or prevalence, of KC in the Turkish population is scant. Nevertheless, the prevalence in our study (40.8%) is much higher than 8.1% and 14.1% values noted more recently [31].

Turkish minorities have a tendency towards 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 [32]. The total number of cases of Turkish origin in our sample was low (2.7%) and these were significantly younger than the Macedonians. Factors such as these may have contributed to the higher odds for KC according to some [30, 32]. 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 was expected due to geographical and habitual proximity. The Albanian community in Macedonia is significantly larger than the Turkish and nurtures relationships with neighbouring 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 that can result in sample bias. The study was performed in Refractive surgery unit of a private hospital, which results in selected group of patients which already have some refractive issues and can avail themselves for treatment in a private setting.

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

Declarations:

Funding:

Authors of the study did not receive any funding for this work.

Conflicts of interest/Competing interests:

The authors report no conflicts of interest concerning this study. The authors have no relevant financial or non-financial interests to disclose. The authors alone are responsible for the content and writing of the paper.

Availability of data and material:

not applicable

Code availability:

not applicable

Autors contribution:

Conceptualization: Fanka Gilevska, Alma Biscevic; Methodology: Fanka Gilevska, Maja Bohac, Biljana Kostovska; Formal analysis and investigation: Fanka Gilevska, Ilir OSmani, Biljana Kostovska; Writing - original draft preparation: Fanka Gilevska; Writing - review and editing: Sudi Patel, Maja Bohac, Smiljka Popovic Suic, Alma Biscevic; Funding acquisition: not applicable; Resources: Smiljka Popovic Suic; Supervision: Maja Bohac, Sudi Patel.

Ethics approval:

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

Consent to participate:

not applicable

Consent for publication:

not applicable

Submission statement:

This submission has not been published anywhere previously and it is not simultaneously being considered for any other publication.

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