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Tobacco smoking in crosslinked keratoconus patients
Tabagisme chez les patients kératoconiques traités par A-CXL

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Running title :

Tobacco smoking in crosslinked keratoconus patients
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Abstract

Purpose: The aim of this study was to evaluate the possibly protective link of smoking in keratoconic patients treated with accelerated cross-linking.

Methods: A telephone survey was conducted among 80 KC patients treated by accelerated crosslinking (A-CXL). The questions focused on general history, possible atopy and smoking habits. Results were compared to those of the general population by indirect standardization by age and sex according to the French national INPES survey.

Results: 62 patients with KC were analyzed. The mean age at diagnosis was 22 years (SD 5). The mean age at which A-CXL was performed was 23 years (SD 6). Daily smokers represented 19 %, occasional smokers 8 %, ex-smokers 21 % and non-smokers 52 %. The mean age at which the patients began smoking was 17 (SD 2) years. Ex-smokers quit at a mean age of 24 (SD 4) years. The observed rates and expected rates of daily smokers were 19 % and 39 % respectively at the time of the survey ($p = 0.01$), 24 % and 35 % at the time of the A-CXL treatment ($p = 0.10$) and 31 % and 35 % at the time of diagnosis ($p = 0.58$). The decrease in the rate of observed daily smokers over time was significant ($p = 0.02$).

Discussion: Our data does not appear to suggest a significant protective effect of smoking on the occurrence of KC. It shows a lesser proportion of smokers in KC patients after A-CXL, but this difference did not exist at the time of KC diagnosis.

Keywords

keratoconus; cross-linking; tobacco use; CXL; A-CXL

Résumé

Le but de cette étude était d'évaluer le lien éventuellement protecteur du tabagisme chez des patients kératocôniques traités par cross-linking accéléré.

Méthodes : Une enquête téléphonique a été menée auprès de 80 patients atteints de KC traités par cross-linking accéléré (A-CXL).

Les questions portaient sur les antécédents généraux, l'atopie éventuelle et les habitudes tabagiques. Les résultats ont été comparés à ceux de la population générale par normalisation indirecte en fonction de l'âge et du sexe, selon l'enquête française INPES.

Résultats : 62 patients atteints de KC ont été analysés. L'âge moyen au moment du diagnostic était de 22 ans (+/- 5). L'âge moyen auquel l'A-CXL a été réalisée était de 23 ans (+/- 6). Les fumeurs quotidiens représentaient 19 %, les fumeurs occasionnels 8 %, les ex-fumeurs 21 % et les non-fumeurs 52 %. L'âge moyen du début du tabagisme était de 17 ans (+/- 2). Les ex-fumeurs ont arrêté à un âge moyen de 24 ans (+/- 4). Les taux observés et attendus de fumeurs quotidiens étaient respectivement de 19 % et 39 % au moment de l'enquête ($p = 0,01$), 24 % et 35 % au moment du traitement par A-CXL ($p = 0,10$) et 31 % et 35 % au moment du diagnostic ($p = 0,58$). La diminution du taux de fumeurs quotidiens observés parmi les patients traités était significative ($p = 0,02$).

Discussion : Nos données ne semblent pas suggérer un effet protecteur significatif du tabagisme sur la survenue de la KC. Il montre une proportion moindre de fumeurs chez les patients atteints de KC après un traitement par A-CXL, mais cette différence n'existe pas au moment du diagnostic de KC.

Mots clefs

Keratocônes ; cross-linking ; intoxication tabagique ; CXL ; A-CXL

Manuscript

Introduction

Keratoconus (KC) is a non-inflammatory, ectatic corneal disorder that affects the central or paracentral part of the cornea.[1] The cornea undergoes progressive thinning and steepening, characterised by conical deformation, causing irregular astigmatism. KC affects predominantly Indians, Pakistanis, Arabs, and Polynesians compared with Caucasian populations.[2] Despite several studies, the exact cause of the disease still remains unclear. Clinical studies have speculated over a heterogeneous multifactorial disorder. KC seems to be associated with atopy,[3] eye rubbing,[4] Down's Syndrome,[5] Leber's congenital amaurosis,[6] and Ehler's Danlos connective disorders.[7] The hereditary pattern is neither prominent nor predictable, but positive family histories have been reported.[8] The estimated incidence among Caucasians is 50/100,000.[9] KC affects both genders, although some studies have not found differences in the prevalence between genders,[10,11] others have found a greater prevalence in females,[12,13] while other investigators have found a greater prevalence in males.[12–14] In an epidemiologic study Spoerl, stated that the incidence of KC in smokers is considerably lower than in the non-smoking population.[15] Hafezi's study reported that chronic smoking increases corneal rigidity in a statistically significant manner.[16] However Ebru et al.[17] showed that corneal biomechanical parameters (Corneal Hysteresis and Corneal resistance Factors) of chronic smokers are more or less similar to those of healthy non-smokers. In addition, a Turkish study led by Yildirim studied the effect of smoking on corneal biomechanics and found no significant difference in corneal biomechanics between smoking and control groups.[18]

With so many studies contradicting each other's, we decided to analyse our KC population and focus on their smoking history rather than their smoking at a fixed point in time. Considering that the French population has one of the highest smoking rates in Europe with 39 % of its population smoking,[19] we decided to focus our study on the Tobacco smoking history among accelerated cross-linked patients to investigate whether any correlation existed between cigarette smoking and the development or progression of KC.

Patients and methods

We conducted a telephone survey among 80 KC patients who were treated from March 2014 until September 2017 by A-CXL within our department. From the 80 people we phoned, 62 answered our survey. Patients were interviewed by an ophthalmologist. They were informed of the objectives of the study and of the type of data collected; they were included only if they gave their oral consent. For under aged patients, parents' consent was asked. The survey was conducted according to the MR-003 methodology of the French National Commission on Informatics and Liberty (CNIL), record number 2061208v0. The study was registered at clinicaltrials.gov (NCT03462355). The questions we asked were patient-related factors, such as family history, allergic history, and finally smoking habits. Family history was considered positive if a first-degree or second-degree relative had been diagnosed with KC. Patients with allergies toward external factors, or anti-allergy medication were marked as positive for atopicity. Patients' smoking habits were recorded and classified. Regular smoker is a person who smokes at least one cigarette per day for more than a year, occasional smoker is a person who smokes one or more cigarettes but not on a daily basis for more than a year, ex-smoker is a person who quit

smoking ≥ 6 months earlier and non-smoker a person who never smoked.[19] Patients were also asked to describe their smoking habits at the time of KC diagnosis, at the time of the A-CXL treatment and at the time of the survey.

Statistical analysis

Quantitative variables were described in terms of means and standard deviations.

Qualitative variables were described as frequencies and percentages. Confidence intervals were computed for percentages according to the continuity-corrected Wald method with alpha risk set at 5 %. Cochran Q test was used to evaluate if the rates of daily smokers over time fitted to a linear trend (paired data). The observed proportions of smokers were confronted to those of the general population by indirect standardization over age, sex based on the 2010 INPES survey data [19] (National French Institute for Prevention and Health Education) ; standardized incidence ratios (SIR) were computed. All analyses were performed with Analysis R software version 3.4.3, and the significance level was set at 0.05. A minimum of 60 observations was needed to assess a linear trend between the 3 smoking rates in a dependent sample with a 5 % difference between each rate. This sample size also allowed estimation of smoking rates with a 15 % precision.

Results

In total 62 patients with KC were analysed. Their characteristics are described in table 1. The mean time between KC diagnosis and A-CXL was 14 months (SD 21), and between A-CXL and the survey 35 months (SD 38). Smoking habits of included patients are described in table 2. Five (8 %) patients stopped daily smoking before KC diagnosis, 4 (7 %) between KC diagnosis and A-CXL treatment and 3 (5 %) between A-CXL and the survey. One patient (2 %) started daily smoking between A-

CXL and the survey. Figure 1 presents observed and standardized daily smokers' proportions along KC history. At the time of the survey, this proportion was 19 % (95 % CI: 9 % – 30 %); at the time of A-CXL it was 24 % (13 % – 36 %); at the time of KC diagnosis, it was 31 % (18 % – 43 %). There was a significant linear decrease in daily smoker rates at these 3 times ($p = 0.02$). The theoretical daily smokers' rates that should have been observed in our sample if the patients had the same smoking habits than the general population were 39 % at the time of the survey, 35 % at the time of A-CXL and 35 % at the time of KC diagnosis. SIR were respectively 0.5, 0.69 and 0.87. The difference between KC patient and general population rates was significant at the time of the survey ($p = 0.01$) but not significant either at the time of A-CXL ($p = 0.10$) nor at the time of KC diagnosis ($p = 0.58$).

Discussion

One of the hallmarks of KC is the change in corneal shape due to the decrease in cross-links between the collagen fibers leading to a decrease in corneal stiffness.[20] Seiler's retrospective study showed a lower incidence of KC in people suffering from diabetes, suggesting that corneal biomechanics are enhanced in diabetic corneas.[21] We know that in diabetes mellitus non-enzymatic glycosylation of proteins (Maillard reaction) occurs and that results in the formation of advanced glycosylation end products (AGEs).[22] Those byproducts can induce cross-links between connective tissue collagen fibers and increase tissue rigidity[21,22]. Other studies have shown that cross-links may be also induced non-enzymatically, by chemical cross-linkers such as formaldehyde or sugar aldehydes, giving diabetes a protective effect on the development or progression of KC.[21,23]

Tobacco like diabetes represents a source of AGEs,[24] cigarette smoke by-products such as nitrogen oxides, nitrite, and formaldehyde,[25,26] can induce cross-links between collagen fibers.[24,27] Cigarette smoking is not recommended due to all the toxic substances found in the smoke.[26] Studies have said that those substances found in smoke, may have an influence on the collagen stability via non-enzymatic CXL, [25,28] while others refuted that theory by demonstrating the exact opposite.[17,18] In our study, the prevalence of daily smoking was significantly lower in KC patients treated by A-CXL in the past few years than in the general population standardized over age and sex. This result is concordant with the study of Spoerl et al. in Germany.[15] The proportion of daily smokers observed in that study was 5 %, and in ours 19 %. Although there are fewer smokers in the German general population[29] than in the general French population[19], the difference between the general population and patients with KC is comparable.

While looking a little deeper, those values tend to gap, the rate of smokers goes from 19 % at the time of the survey, to 24 % at the time of CXL procedure and ends up at 31 % at the time of KC diagnosis. In their study, Spoerl et al. did not mention when were the patients interviewed and at what moment in time were they smoking. As seen in our study, those elements are very important because the entire results can be interpreted differently at various moments in time. With similar daily smoker rates at the time of KC diagnosis, our study suggests that smoking habits are not linked with the appearance of KC. However, since our study is retrospective observational, it is hard to tell if the evolution of KC is explained by a decrease in smoking or if a decrease of smoking is explained by the evolution of KC. The decrease in smoking habits observed after CXL is not related to medical instructions in this case. The decreasing values observed as patients were diagnosed, then treated could be

explained by the fact that patients with KC become aware of the disease and try to maintain a healthy lifestyle (e.g., without smoking).

This kind of modification of smoking habits after illness has already been described.[30] Prospective studies will be needed to confirm this hypothesis. During the telephone survey, patients explained the main factors that led them to the decrease of tobacco usage. The most notable reasons were : Pregnancy, arrival of a new-born baby into the family, appearance of health issues related to smoking and lastly achievement for a personal reason. Similar behaviours are observed among patients in the literature [31]. The limitation of our study is the lack of a control group. A control group would have allowed us to conduct a more refined comparison of smoking rates between patients with and without KC. However, as KC frequency in the general population is low (9), the comparison to general population is a valid approach. Age and sex are dealt with indirect standardization. Smoking habits are also influenced by socio-economic level. In comparison to the French population[19], the patients included in the survey had less often master's or degree diploma. This should be associated with higher rates of smoking [19] and thus comfort our interpretation that KC is not associated with high smoking rates at the beginning of the disease. However, a third of the patients had not finished their studies at the time of the survey. If we consider that all of them obtain the diploma they are studying for, the rates become similar to those of the general population. Having done a retrospective study opens us to the risk of memory bias, poor data quality but nevertheless, the telephone surveys were conducted by a resident doctor who had a good understanding of the covered topic, and the contact with the patients was overall very good (giving us a good quality data). A memory or interview bias would have led to underestimated smoking rates. The rate at KC diagnostic being similar to

the one expected in general population suggests that this bias might have been avoided. A memory bias could have brought uncertainty concerning history of smoking (age at start or stop). This can be expected as a non-differential bias, leading to loss in estimates precision rather than in over- or under-estimations.

In conclusion, this study does not corroborate the hypothesis of a protective effect of smoking on the occurrence of KC. While our data shows a lesser proportion of smokers in KC patients after A-CXL, this difference did not exist at the time of KC diagnosis. We can speculate that smoking habits are changing in response to KC occurrence rather than KC occurrence being influenced by smoking habits. This could be confirmed by studying a prospective cohort.

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Figures legend

Figure 1: Comparison of the proportions of daily smokers (and their linear trends) between patients with keratoconus and general population at three different times (indirect standardization over age and sex, according to the 2010 INPES survey [19]).

Tables

Table 1. Description of the demographical and clinical characteristics of the 62 keratoconous patients included in the survey.

Characteristics	Mean +/- SD	N (%)
Age (Yrs)	26 +/- 7	
Age at time of A-CXL (Yrs)	23 +/- 6	
Age at time of KC diagnosis (Yrs)	22 +/- 5	
Sexe (F)		21 (34)
Highest diploma		
Middle school or no diploma		10 (16)
Professional diploma		12 (19)
High school		23 (37)
Degree		11 (16)
Master's		5 (10)
Doctorate		1 (2)

Table 2. Description of the smoking habits of the 62 keratoconous patients included in the survey.

Smoking habits	Mean +/- SD	N (%)
Daily smoker		12 (19)
Occasional smoker		5 (8)
Ex-smoker		13 (21)
Non-smoker		32 (52)
Passive smoker		43 (69)
smokers and ex-smoker (N = 30)		
Smoking onset age	17 +/- 2	
Duration of smoking	7 +/- 6	
Number of daily cigarettes	7,5 +/- 6	
Smoking stopping age (Ex-smoker, N = 13)	24 +/- 4	

Figure 1

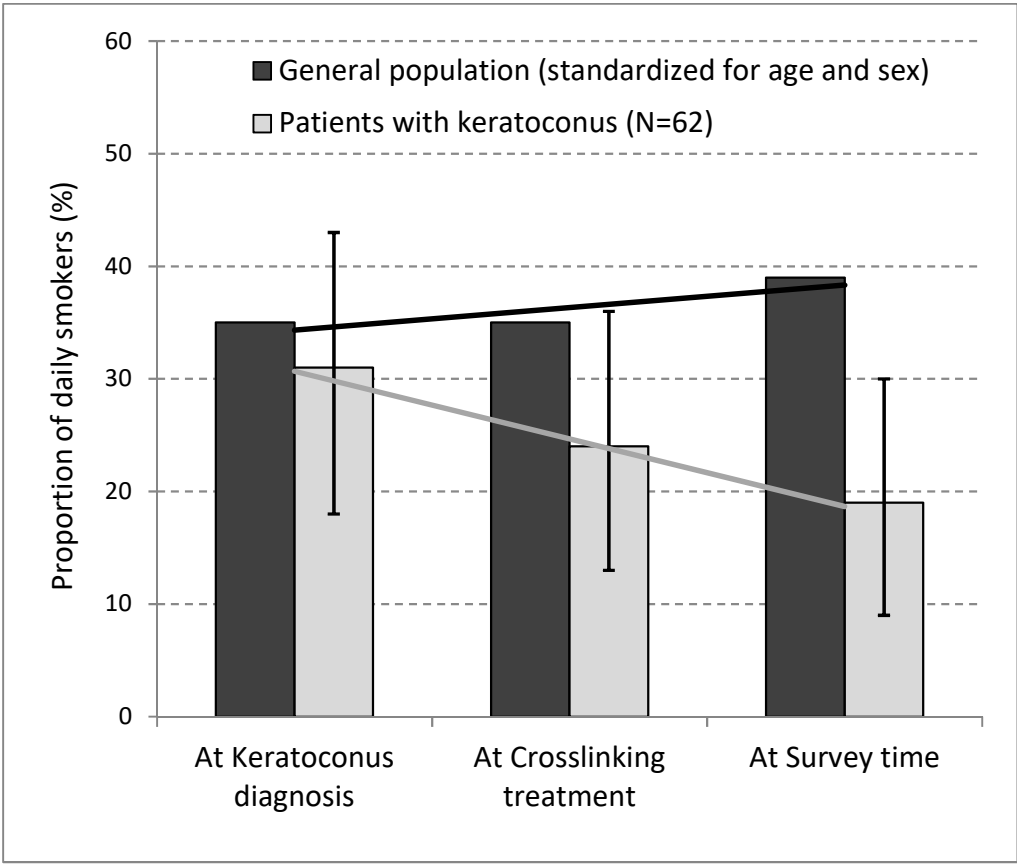


Figure 1. Comparison of the proportions of daily smokers (and their linear trends) between patients with keratoconus and general population at three different times (indirect standardization over age and sex, according to the 2010 INPES survey [19]).