Cigarette Smoking is Negatively Associated With Keratoconus

Eberhard Spoerl, PhD; Frederik Raiskup-Wolf, MD; Eberhard Kuhlisch; Lutz E. Pillunat, MD

ABSTRACT

PURPOSE: To investigate a correlation between cigarette smoking and keratoconus.

METHODS: Patients with keratoconus who were treated with corneal collagen cross-linking from June 2006 to November 2007 were asked about their smoking habits. A person smoking a minimum of two cigarettes per day for more than 1 year was classified as a smoker.

RESULTS: A total of 180 patients with keratoconus (mean age 28±9 years [range: 15 to 41 years]) were asked about their smoking habits. One hundred seventy-one (95%) were non-smokers and only 9 (5%) were smokers (95% confidence interval, 2.31 to 9.28). Using the chi-square test, a significant correlation was found between non-smokers and keratoconus ($P<.001$).

CONCLUSIONS: In this group of patients with keratoconus, few were smokers. Cigarette smoke contains toxic substances. Consequently, people are advised not to smoke. However, we speculate that the by-products of cigarette smoke may lead to cross-linking of collagen, which in the cornea, may prevent the development and progression of keratoconus. [*J Refract Surg*. 2008;24: xxx-xxx.]

One of the main symptoms of keratoconus is the change in corneal shape due to its reduced stiffness, which leads to impaired visual acuity. The reduction of cross-links between the collagen fibers may cause these biomechanical alterations. An artificial increase of cross-links by riboflavin and ultraviolet A (UVA) is a promising approach for the treatment of keratoconus. Previous studies have shown that cross-links may also be induced non-enzymatically by chemical cross-linkers such as formaldehyde or sugar aldehydes.[1] Thus, diabetes has a protective effect on the development or progression of keratoconus.[2,3] For the stiffening of collagen and formation of cross-links, free oxygen radicals are a prerequisite. A stiffening effect in the skin and blood vessels was observed among patients who smoked.[4,5] However, does smoking also influence the corneal biomechanics?

The aim of the present study was to investigate whether any correlation exists between cigarette smoking and the development or progression of keratoconus.

PATIENTS AND METHODS

In our clinical study concerning the cross-linking treatment of keratoconus with riboflavin/UVA,[6] patients were asked about their smoking habits. These patients came from all over Germany for the cross-linking treatment, as it was only performed in Dresden at that time. From June 2006 to November 2007, 180 patients with keratoconus who were treated with riboflavin/UVA cross-linking in our department were questioned. Those who smoked at least 2 cigarettes daily for more

From the Department of Ophthalmology (Spoerl, Raiskup-Wolf, Pillunat) and Institute of Medical Informatics and Biometry (Kuhlisch), Technical University Dresden, Germany.

The authors have no commercial or proprietary interest in the materials presented herein.

Presented in part at the International Congress of Corneal Cross Linking; December 7-8, 2007; Zurich, Switzerland.

Correspondence: Eberhard Spoerl, PhD, Dept of Ophthalmology, Carl Gustav Carus University Hospital, Fetscherstr 74, 01307 Dresden, Germany. Tel: 49 351 458 3763; Fax: 49 351 458 4335; E-mail: eberhard.spoerl@uniklinikum-dresden.de

TABLE

Percentage of Smokers and Non-smokers in Average German Population and Patients With Keratoconus

	Average Population	Keratoconus Group
Smokers	30	5
Non-smokers	70	95

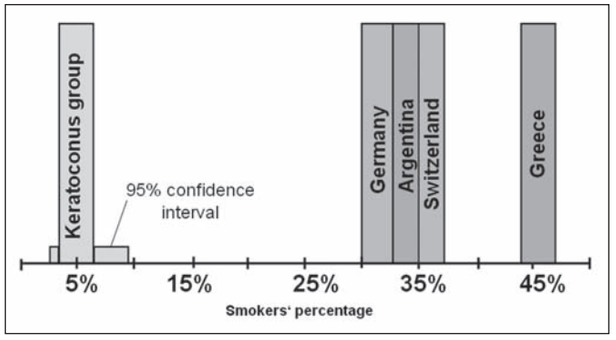

Figure. Number of smokers in the keratoconus group compared with the number of smokers in several countries.

than 1 year were classified as smokers. The numbers of smokers and non-smokers were compared with corresponding statistical values of the German population from the "Statistisches Bundesamt" (Office of National Statistics of Germany) and German literature.

RESULTS

Among the 180 patients with keratoconus, 171 (95%) were non-smokers and only 9 (5%) were smokers (95% confidence interval, 2.3 to 9.3). Mean patient age was 28±9 years (range: 15 to 41 years).

As a comparison, we looked at the number of smokers in the German population aged between 15 and 30 years (Table). Approximately 30% to 35% are smokers.[7] Females smoke slightly less. There were no regional differences in smokers in Germany. The number of smokers found in the literature is even higher. Approximately 47% of young men aged between 17 and 30 years in Greece are smokers[8]; this figure in Switzerland is 35%.[9] A population-based survey of 43,863 participants aged between 20 and 34 years in Argentina shows that approximately 34% of the population smokes.[10] The number of smokers in other countries at this age is approximately 30% (Fig). There is a significant correlation between non-smokers and keratoconus (chi-square test, $P<.001$). Apparently, the number of smokers is reduced in the keratoconus group compared to the number of smokers in the population in several countries.

DISCUSSION

It is well known that cigarette smoking is noxious due to the toxic substances contained in the smoke. Lu et al[11] found over 3000 organic compounds, including 60 known carcinogens. Cigarette smoking is responsible for more than 85% of lung cancers and is also associated with cancers of the mouth, pharynx, larynx, and esophagus. However, some of these substances may have an influence on the collagen stability via non-enzymatic cross-linking.

In this study, we found that the number of smokers in the keratoconus group is lower compared to the corresponding statistical value. The average German population aged 15 to 30 years shows that at least 30% are smokers. In our keratoconus group, only 5% were smokers. This difference can not be explained by the fact that patients with keratoconus are aware of the disease and try to maintain a healthy lifestyle (eg, without smoking). The disease is mostly found accidentally during routine examination. A weakness of the study is the lack of a population control.

There are four possible explanations for the lower rate of smokers in the group of patients with keratoconus.

- Cigarette smoke contains low molecular weight carbonyl compounds such as formaldehyde, acetaldehyde, glyoxal, methylglyoxal, and malonaldehyde.[12] Baker[13] showed that formaldehyde is a main toxic product in cigarette smoke. These compounds act as chemical cross-linkers in the skin but also in the cornea.[1] Madhukumar et al[14] found that when the skin of rats is exposed to cigarette smoke it shows a higher degree of cross-links and a higher resistance to collagenase. Krishnaiah et al[15] found that tobacco smoking was strongly associated with a higher prevalence of nuclear cataract. The major damaging mechanism seems to be oxidative stress caused by reactive oxygen species.
- Smoking increases the content of advanced glycation end products, which act similar to the sugar aldehydes in the formation of advanced glycation end products in diabetes.[2,3] Advanced glycation end products are reactive, cross-linking products resulting from the reaction of reducing sugar and the amino group of proteins.[16] Advanced glycation end products have been shown to cross-link connective tissue collagen, which serves to increase connective tissue rigidity.[17] Glycotoxins are far more potent than glucose. Tobacco products may be a source of reactive glycation products capable of promoting advanced glycation end products formation. Ciga-

rette smoke is an exogenous source of reactive glycation products.[18,19]

- During tobacco smoking, nitrogen oxides and nitrite are released at a high level, which also may produce cross-links and modify collagen proteins.[20,21]
- If estrogen plays a role in the development of keratoconus,[22,23] smoking can reduce the level of estrogen.[24] Cigarette smoking increases hydroxylation of estradiol, as well as inhibition of the enzyme aromatase,[25,26] which converts androgens to estrogens, creating a relative hypo-estrogenic state. Epidemiological results indicate that women who smoke cigarettes are relatively estrogen-deficient.[27] Female smokers have an early natural menopause and a lower risk of cancer of the endometrium. Smoking appears to alter the metabolism of estradiol, leading to enhanced formation of the inactive catechol estrogen.[28] Smoking influences estrogen metabolism and appears to attenuate the effect of estrogen.

Other investigations have shown that smoking has an influence on tissue metabolism and biomechanics. Smoking leads to a protein modification in the human lens and accelerates cataract development.[15,29] Recently, another link was found between smoking and myopia.[30] If one or both parents smoke, their children were found to have a lower myopia prevalence and a more hyperopic mean refraction than those children whose parents never smoked.[30] All of these facts indicate that smoking influences biochemical processes[31] and may change the biomechanics of the cornea. We speculate that smoking may inhibit or suppress the triggering factors of keratoconus and lead to a decreased rate or severity of keratoconus. Further studies are needed to investigate the biochemical mechanism.

Many health risks of tobacco smoking prohibit the recommendation of exposure to cigarette smoke in patients with keratoconus. This relationship between cigarette smoking and keratoconus should not be a treatment proposal or suggestion because of irreversible side effects and extensive organ damage. However, this relationship may contribute to an explanation of the pathophysiological reasons for keratoconus development.

REFERENCES

1. Spoerl E, Seiler T. Techniques for stiffening the cornea. *J Refract Surg*. 1999;15:711-713.
2. Seiler T, Huhle S, Spörl E, Kunath H. Manifest diabetes and keratoconus: a retrospective case-control study. *Graefes Arch Clin Exp Ophthalmol*. 2000;238:822-825.
3. Kuo IC, Broman A, Pirouzmanesh A, Melia M. Is there an association between diabetes and keratoconus? *Ophthalmology*. 2006;113:184-190.
4. Morita A. Tobacco smoke causes premature skin aging. *J Dermatol Sci*. 2007;48:169-175.
5. Mahmud A, Feely J. Effect of smoking on arterial stiffness and pulse pressure amplification. *Hypertension*. 2003;41:183-187.
6. Raiskup-Wolf F, Hoyer A, Spoerl E, Pillunat LE. Collagen crosslinking with riboflavin and UVA-light in keratoconus: long-term results. *J Cataract Refract Surg*. 2008;34:796-801.
7. Junge B, Nagel M. Smoking behavior in Germany [German]. *Gesundheitswesen*. 1999;61:S121-S125.
8. Psathakis K, Bouros D, Vlasserou F, Tzanakis N, Slafakas NM. Relationship between the age at which smoking begins and frequency of smoking in young males in Greece. *N Engl J Med*. 1991;325:968-969.
9. Health: potential widespread causes for health problems. In: Schäfer G, Feith M, Fritz M, Johansson Augier A, Wieland U, eds. *Europe in Figures: Eurostat Yearbook 2006-07*. Available at: http://epp.eurostat.ec.europa/cache/ITY_OFFPUB/KS-CD-06-001/EN/KS-CD-06-001-EN.PDF. Accessed
10. Martinez E, Kaplan CP, Guil V, Gregorich SE, Mejia R, Pérez-Stable EJ. Smoking behavior and demographic risk factors in Argentina: a population-based survey. *Prev Control*. 2006;2:187-197.
11. Lu X, Cai J, Kong H, Wu M, Hua R, Zhao M, Liu J, Xu G. Analysis of cigarette smoke condensates by comprehensive two-dimensional gas chromatography/time-of-flight mass spectrometry I acidic fraction. *Anal Chem*. 2003;75:4441-4451.
12. Fujioka K, Shibamoto T. Determination of toxic carbonyl compounds in cigarette smoke. *Environ Toxicol*. 2006;21:47-54.
13. Baker RR. The generation of formaldehyde in cigarettes: overview and recent experiments. *Food Chem Toxicol*. 2006;44:1799-1822.
14. Madhukumar E, Vijayammal PL. Influence of cigarette smoke on cross-linking of dermal collagen. *Indian J Exp Biol*. 1997;35:483-486.
15. Krishnaiah S, Vilas K, Shamanna BR, Rao GN, Thomas R, Balasubramanian D. Smoking and its association with cataract: results of the Andhra Pradesh Eye Disease Study from India. *Invest Ophthalmol Vis Sci*. 2005;46:58-65.
16. Cerami C, Founds H, Nicholl I, Mitsuhashi T, Giordano D, Vanpatten S, Lee A, Al-Abed Y, Vlassara H, Bucala R, Cerami A. Tobacco smoke is a source of toxic reactive glycation products. *Proc Nat Acad Sci USA*. 1997;94:13915-13920.
17. Bailey AJ, Paul RG, Knott L. Mechanisms of maturation and aging of collagen. *Mech Aging Dev*. 1998;106:1-56.
18. Nicholl ID, Stitt AW, Moore JE, Ritchie AJ, Archer DB, Bucala R. Increased levels of advanced glycation endproducts in the lenses and blood vessels of cigarette smokers. *Mol Medicine*. 1998;4:594-601.
19. Nicholl ID, Bucala R. Advanced glycation endproducts and cigarette smoking. *Cell Mol Biol*. 1998;44:1025-1033.
20. Paik DC, Dillon J, Galicia E, Tilson MD. The nitrite/collagen reaction: non-enzymatic nitration as a model system for age-related damage. *Connect Tissue Res*. 2001;42:111-122.
21. Paik DC, Saito LY, Sugirtharaj DD, Holmes JW. Nitrite-induced cross-linking alters remodeling and mechanical properties of collagenous engineered tissues. *Connect Tissue Res*. 2006;47:163-176.
22. Spoerl E, Zubaty V, Raiskup-Wolf F, Pillunat LE. Oestrogen-induced changes in biomechanics in the cornea as a possible reason for keratectasia. *Br J Ophthalmol*. 2007;91:1547-1550.
23. Zylberberg C, Seamon V, Ponomareva O, Vallala K, Deighan M, Azzarolo AM. Estrogen up-regulation of metalloproteinase-2 and -9 expression in rabbit lacrimal glands. *Exp Eye Res*. 2007;84:960-972.
24. Mueck AO, Seeger H. Smoking, estradiol metabolism and hormone replacement therapy. *Arzneimittelforschung*. 2003;53:1-11.

25. Osawa Y, Tochigi B, Tochigi M, Ohnishi S, Watanabe Y, Bullion K, Osawa G, Nakabayashi Y, Yarborough C. Aromatase inhibitors in cigarette smoke, tobacco leaves and other plants. *J Enzyme Inhib*. 1990;4:187-200.
26. Trüeb R M. Association between smoking and hair loss: another opportunity for health education against smoking? *Dermatology*. 2003;206:189-191.
27. Baron JA, La Vechia C, Levi F. The antiestrogenic effect of cigarette smoking in women. *Am J Obstet Gynecol*. 1990;162:502-514.
28. Transavatdi K, McClain B, Herrington DM. The effects of smoking on estradiol metabolism. *Minerva Ginecol*. 2004;56:105-114.
29. Mukesh BN, Le A, Dimitrov PN, Ahmed S, Taylor HR, McCarty CA. Development of cataract and associated risk factors: the Visual Impairment Project. *Arch Ophthalmol*. 2006;124:79-84.
30. Stone RA, Wilson LB, Ying GS, Liu G, Criss JS, Orlow J, Lindstrom JM, Quinn GE. Associations between childhood refraction and parental smoking. *Invest Ophthalmol Vis Sci*. 2006;47:4277-4287.
31. Satici A, Bitiren M, Ozardali I, Vural H, Kilic A, Guzey M. The effects of chronic smoking on the ocular surface and tear characteristics: a clinical, histological and biochemical study. *Acta Ophthalmol Scand*. 2003;81:583-587.