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The effect of statin use on lens density as assessed by pentacam hr® lens densitometry in adults

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Abstract

Objective: To investigate the association between statin use and cataract development by using Pentacam HR Scheimpflug camera system.

Material and Methods: Total 208 age and sex matched participants were included in this prospective, case-control study. 104 long-term statin users as study group and 104 non-statin users as control group constituted to the study. Lens densitometry measurements were performed with the Pentacam HR® (Oculus, Wetzlar, Germany) from three areas (anterior, nuclear, and posterior). These measurements were compared between the groups.

Results: There were no significant difference at the basic clinical variables (p=0.121, p=0.778). The mean duration of statin use of the study group was 5,4±4,3 years. The mean value of lens densitometry measurement at nuclear area tended to be lower in statin users than controls, but difference was not statistically significant (9.20±1.00 vs 9.35±1.20; p:0.346). However, the mean lens densitometry values at the anterior and posterior areas of statin users were found to be significantly higher than controls (10.44±1.32 vs 9.16±1.09;p<0.001; 7.86±0.49 vs 7.63±0.38; p<0.001,respectively).

Conclusion: The current study finds that long-term statin use seems to be associated with an increased risk of cortical cataracts (anterior-posterior) but not incidence of nuclear cataracts

Key Words: Statin, Cataract, Pentacam HR®.

Introduction

Cataract is the leading cause of low vision and blindness in the world (1). Because of the growing elderly population, the incidence of cataract is likely to increase. However, the exact mechanisms and pathogenesis of cataract formation are not completely understood. Therefore, investigating the risk factors for cataract development is crucial with its both medical and economical aspects (2).

Statins are widely prescribed drugs for their lipid-lowering effect. They also may have antioxidant effects and anti-inflammatory actions on the lens (3). While oxidative damage to the lens epithelium may induce cataract formation, statins may be protective against cataractogenesis. However, recent studies showed controversial results, with some suggesting an increased risk of cataracts with statin use (2,4,5) while others appear to show a beneficial effect of statins on cataract risk (5,6,7).

Another large study demonstrated that recent longer-term statin use was protective against cataract surgery in younger patients (50-64 years of age), while shorter-term use was associated with an increased risk of surgery (8). In the current study, we aimed to evaluate the effect of statin use on lens density by using Pentacam HR Scheimpflug camera system which provides objective and quantitative lens densitometry (LD) analysis..

Material and Methods

The 104 long-term statin users (study group) and 104 non-statin users (control group) were enrolled in this prospective, case-control study. The participants were matched for age and sex between groups. Informed consent was obtained from all the volunteers. The study was carried out in accordance with the tenets of the Declaration of Helsinki, and was approved by the institutional ethical committee.

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The exclusion criteria were; the presence of any pathology of the anterior segment and fundus, any refractive errors within ± 3 diopters spherical equivalent, the presence of systemic diseases such as diabetes mellitus, hypertension and connective-tissue diseases, the history of ocular trauma and ocular surgery, the history of chronic ocular diseases such as glaucoma, keratoconus and uveitis, the history of smoking or current smokers, the history of long-term (more than 1 month) use of systemic or ocular corticosteroids.

The following examinations were applied to all the participants in the study; visual acuity, anterior segment biomicroscopy, intraocular pressure, dilated fundus examination and Scheimpflug anterior segment analysis.

LD measurements were performed with Pentacam HR after maximal dilation with 2,5% phenylephrine and 1% tropicamide ophthalmic solution. Only the right eyes of subjects were included in study. The right eye of each subject was scanned twice by one experienced observer.

To minimize operator-dependent variables, Pentacam's automatic release mode was used. In this mode, the instrument automatically determines when correct focus and alignment with the corneal apex have been achieved and then performs a scan. Automatic release and 50-picture 3-dimensional (3D) scan modes were used for measurements. Images of 90-270º were assessed.

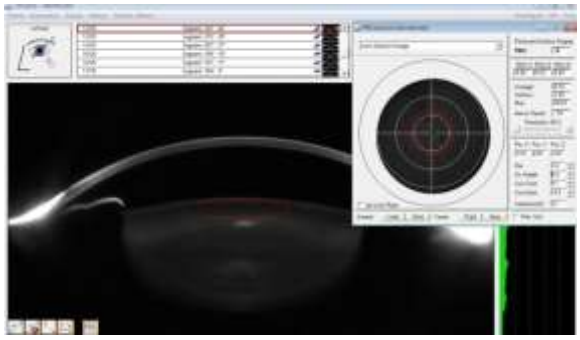

Figure 1: Anterior area (anterior subcapsular and cortical) measurement is shown.

Figure 2: Nuclear area measurement is shown in the figure.

While it is difficult to identify the exact boundaries of anterior subcapsular and cortical areas from the images, we measured the lens density from three areas. These areas were anterior (anterior subcapsular and anterior cortical), nuclear, and posterior (posterior subcapsular and posterior cortical).

To avoid measurement artefacts and perform a standard scan, we used 2,4 mm (horizontal) x 0,8 mm (vertical), 3,6 mm (horizontal) x 2.1 mm (vertical) and 2,4 mm (horizontal) x 0,6 mm (vertical) 3D body for anterior (Figure 1), nuclear (Figure 2) and posterior areas (Figure 3), respectively. After this process, Pentacam HR software calculated average values of 3D lens density automatically as seen in the figures in the top right corner.

All statistical analysis was carried out using SPSS 17.0 (SPSS, Chicago, Illinois, USA). Continuous variables were given as mean ± SD and categorical variables were defined as percentages. Normality of continuous variables' distribution was tested using Kolmogorov-Smirnov test. Normally distributed continuous variables were compared using independent samples t test. Other continuous variables were compared using Mann-Whitney U test. All analysis were two sided and considered significant at a p value of < 0.05.

A multiple linear regression model was used to identify independent predictors of LD. Also the effects of gender and age on LD were adjusted using two-way ANOVA and ANCOVA tests, respectively.

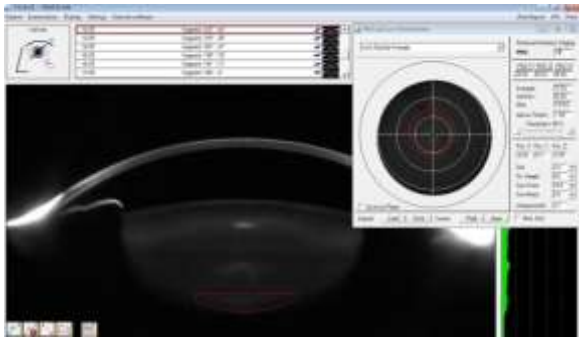

Figure 3: Posterior area (posterior subcapsular and posterior cortical) measurement is shown.

Results

Our study sample involved 104 long-term statin users and 104 healthy non-statin users. The study and control groups were similar in terms of gender and age. Study populations' baseline characteristics and demographics are given in table 1. The mean age of the study population was 58,4±8.4 years. Mean duration of statin use was 5,4±4,3 years. Among the statin users, a total of 56 patients (53.8%) had been recently using atorvastatin and 48 patients (46.1%) had stated rosuvastatin use.

Table 2 shows the results of mean LD values in the three areas in the study and control groups. The mean value of LD measurement at nuclear area tended to be lower in statin user group than controls, but difference was not statistically significant (9.20±1.00 vs 9.35±1.20; p:0.346). However, the mean LD value at the anterior area of study group was found to be statistically significantly higher (10.44±1.32 vs 9.16±1.09; p<0.001).

The mean LD value at the posterior area was also significantly higher in statin users (7.86±0.49 vs 7.63±0.38; p<0.001). In the subgroup analysis of LD measurements according to statins' type, no statistically significant difference existed between atorvastatin and rosuvastatin (Table 3). In order to eliminate the effect of gender and age on LD measurements, we have performed two-way ANOVA and ANCOVA tests, respectively. We found that while age has a statistically significant effect on the LD values of three areas (p<0.001), gender has not a statistically significant effect on the posterior area LD (p:0.089) but has an effect on the anterior and nuclear areas' LD measurements (p<0.001). Therefore, we performed a multiple linear regression model to identify regression coefficients of LD measurements. We observed that statin use was found to be more associated with LD values than gender and age (Table 4).

Table 1: Demographic characteristics of study and control groups.

	Study Group (N=104)	Control Group (N=104)	P value
Age (Mean [SD])	58,4 (8.4)	56,8 (6.0)	0.121
Sex (Male [%])	63 (60.6)	61 (58,7)	0.778*
Statin use (year)	5,4±4,3	-	
Statin agent type			
Atorvastatin (N[%])	56 (53.8)	-	
Rosuvastatin (N[%])	48 (46.1)	-	

*Mann-Whitney U

Table 2: LD measurements in the three areas in both groups.

	Study Group (N=104)	Control Group (N=104)	P value**
Anterior area (mean[SD])	10.44±1.32	9.16±1.09	<0.001
Nuclear area (mean[SD])	9.20±1.00	9.35±1.20	0.346
Posterior area (mean[SD])	7.86±0.48	7.63±0.38	<0.001

**Student t test

Table 3: Subgroup analysis of LD measurements in the three areas according to statins' type.

	Atorvastatin (N=56)	Rosuvastatin (N=48)	P value***
Anterior area (mean[SD])	10.41±1.29	10.47±1.36	0.816
Nuclear area (mean[SD])	9.16±0.88	9.25±1.14	0.672
Posterior area (mean[SD])	7.92±0.50	7.78±0.46	0.150

***Student t test

Table 4: Regression coefficients of LD measurements in the three areas in a multiple linear regression model.

	Anterior area		Nuclear area		Posterior area	
	B (Std Error)	P value	B (Std Error)	P value	B (Std Error)	P value
Statin use	1.262 (0.158)	<0.001	0.175 (0.140)	0.211	0.223 (0.059)	<0.001
Gender	0.594 (0.162)	<0.001	0.374 (0.142)	0.009	0.099 (0.060)	0.102
Age	0.037 (0.009)	<0.001	0.049 (0.008)	<0.001	0.013 (0.003)	<0.001

Discussion

There are several studies about the relationship between statin use and cataract formation. However, the findings in these studies are inconsistent and controversial. While some of them did not report an association between statin use and cataract (9,10,11,12), some found a protective effect of statins on cataract (5,6,7). Recently, few studies demonstrated an increased risk of cataract associated with statins (2,4,5,13,14). The majority of these studies are observational and dependent on the medical records derived from the national databases. Since cataract is not an ''all-or-nothing disease: there is a continuous spectrum of severe cataract to minor opacities that would only be found on detailed examination'' (12), it is likely therefore that early cataracts would have been missed in these studies. This may have caused a '' misclassification bias''. Therefore, we believe that our study differs with its unique design from these studies.

The results of this study suggest that statin use is significantly associated with anterior and posterior lens opacities (anterior-posterior subcapsular or cortical) but not incidence of nuclear cataracts. This difference may be due to the reality that varied etiological factors are related to specific cataract subtypes (5). For example, nuclear cataract is associated with oxidative stress, especially in the pathogenesis of age related cataract, cortical cataract is associated with UV exposure (15), and posterior subcapsular cataract with steroid use (16). Thus, it is possible that protective factors may also differ (5).

As previously reported, a protective effect of statins on nuclear cataract is biologically plausible because oxidative stress (17,18) and inflammation (19) have been shown to be related to nuclear cataract, and statins have been reported to counter such effects (20,21).

On the other hand, in another study it was shown that statins were differentially distributed in the lens, particularly a higher concentration was achieved in the cortex than in the nucleus of the beagles' lenses (22). This finding may explain why higher cortical cataract incidence was found in our study. In addition; Cenedella (23) hypothesized that the inhibition of cholesterol biosynthesis by statin medications prevents proper epithelial cell development within the crystalline lens. The lens' epithelial cells require high cholesterol levels to maintain transparency of the lens. Increased rates of cataract among animals and humans with hereditary cholesterol deficiency have been observed in another study (24). Recently, lanosterol synthase deficiencies in two families with extensive congenital cataracts were reported (25). The researchers (25) mentioned that lanosterol treatment could reduce cataract severity and increase transparency in dissected rabbit cataractous lenses in vitro and cataract severity in vivo in dogs. Since lanosterol is synthesized by lanosterol synthase in a key cyclization reaction of a cholesterol synthesis pathway, statins may be leading to cataract formation by inhibiting this pathway.

Actually, the results of our study do not conflict entirely with the other studies' results, on the contrary, the results are complementary with them. For example, The Beaver Dam Eye Study reported a lower risk of nuclear cataract in statin users (5). A similar risk reduction was observed in the Blue Mountains Eye Study (6). However, a insignificant increased risk of cortical cataract (5) and posterior subcapsular cataract (6) were also reported in these studies respectively in a similar way to our results. Our study differs from these trials with our cataract assessment technique and in our opinion this is one of the strengths of our study. Having not been using data from medical records, we may have reduced the risk of '' misclassification bias''. Sure, encountering with some artefacts in the LD analysis process is possible but we have tried to avoid from these artefacts by using a standardization method in the measurement procedure. Nonetheless, some factors such as back scattering of light from the anterior lens area, shadows and light attrition may decrease the amount of light transmitted to the posterior pole of the lens and this may have caused nuclear and posterior area to appear less dense (26). Another limitation of the current study is that it is a not prospective cohort study. We have performed two-way ANOVA, ANCOVA and multiple regression analysis in order to evaluate the effect of gender and age on LD. Although statin use was still found to be more effective on LD than age and gender, our results may have been influenced by some other unpredictable factors. We have excluded the patients with any refractive errors within ± 3 diopters spherical equivalent and any systemic diseases such as diabetes mellitus, hypertension and connective-tissue diseases. Nevertheless, we know that anti-hyperlipidemic treatment is used for cardiovascular disorders and the patients usually have comorbidities. Surely, some factors like these may have affected our results

Conclusion

In conclusion, statins seem to be associated with an increased risk of cortical cataracts (anterior-posterior) but not incidence of nuclear cataracts. Nonetheless, the exact mechanism of the effect of statins in cataractogenesis is still unknown. Certainly, statins are very effective medications and the mainstay in the treatment of heart disease; therefore, side effects are expected. To identify the exact relationship, further double-blinded randomize controlled trials must be designed.

Conflict of Interest: The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical issues: All Authors declare that Originality of research/article etc... and ethical approval of research, and responsibilities of research against local ethics commission are under the Authors responsibilities. The study was completed due to defined rules by the Local Ethics Commission guidelines and audits.

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