Cataracts and Subclinical Carotid Atherosclerosis in Older Adults
— A Cross-Sectional Study of the HEIJO-KYO Cohort —

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Background: Decreased light reception because of cataracts leads to potential circadian misalignment, resulting in exacerbation of atherosclerosis; however, little is known about the association between cataracts and atherosclerosis in populations.

Methods and Results: In this cross-sectional study, cataracts were graded using slit lamp biomicroscopy with the Lens Opacities Classification System III and carotid atherosclerosis was assessed based on carotid intima-media thickness (IMT) measured using ultrasonography of the common carotid artery in 442 elderly participants (mean age, 70.0 years). Cataract was defined as nuclear cataract grade ≥3.0, cortical cataract grade ≥2.0, or posterior subcapsular cataract grade ≥2.0 in both eyes. The mean and maximal carotid IMT was 0.86±0.15 mm and 1.07±0.29 mm, respectively. In multivariable analysis adjusted for potential confounders, the mean and maximal carotid IMT were significantly greater in the cataract group than in the non-cataract group by 0.04 mm (95% confidence interval (CI), 0.01–0.06) and 0.07 mm (95% CI, 0.01–0.12), respectively. Logistic regression analysis adjusted for confounders revealed a significantly higher odds ratio for carotid atherosclerosis (maximal carotid IMT ≥1.1 mm) in the cataract group than in the non- cataract group (odds ratio, 1.78; 95% CI, 1.14–2.78).

Conclusions: Cataracts may be independently associated with subclinical carotid atherosclerosis in the elderly population, indicating a need for further prospective studies.

Key Words: Atherosclerosis; Cataracts; Carotid intima-media thickness; Circadian rhythm; Epidemiology

Cataract is an aging-related cloudiness in the crystalline lens. It is highly prevalent among the elderly and a leading cause of visual impairment and blindness. Although visual acuity is impaired mostly in advanced cataracts, light transmission to the retina decreases even in early-stage cataracts; 70-year-olds without advanced cataracts are estimated to have approximately 20% of the light transmission to the retina present in healthy teenagers. In addition, cataract is characterized by decreased reception of shorter wavelength light, particularly that below 500 nm, to which the intrinsically photosensitive retinal ganglion cells are most sensitive. These cells are primary light sensors associated with circadian biological rhythms. Replacement of clouded crystalline lenses with intraocular lenses increases light transmission capacity to the retina, resulting in circadian alignment, such as increased melatonin secretion. Thus, light reception sensitive to circadian biological rhythms is likely to significantly decrease in patients with early-stage cataracts.

Circadian biological rhythmicity is controlled by the suprachiasmatic nucleus of the master biological clock. Epidemiological studies suggest that shift work disrupts circadian function and is associated with atherosclerosis-related diseases, such as hypertension, obesity, dyslipidemia, diabetes, and cardiovascular diseases. Previous studies have revealed a cellular basis underlying the association between disrupted circadian function and cardiovascular systems; clock gene mutations induce atherosclerosis and altered vascular endothelial function.

Considering all these findings, we hypothesized that decreased light reception with cataracts leads to potential circadian misalignment, resulting in atherosclerosis exacerbation in elderly individuals. An Asian nationwide cohort study has suggested higher cardiovascular disease risk in cataract patients; however, subclinical-level literature evidence of such an association is limited.

Carotid artery intima-media thickness (IMT) is a widely accepted marker of subclinical atherosclerosis, and its...
measurement in the common carotid artery (CCA) using ultrasonography can strongly predict future cardiovascular diseases independent of conventional risk factors. In this cross-sectional study, we evaluated ocular status using slit lamp biomicroscopy and CCA–IMT via ultrasonography. We hypothesized that CCA–IMT was associated with the presence of cataracts in elderly individuals.

Methods
Participants
The baseline survey of the “Housing Environments and Health Investigation among Japanese Older People in Nara, Kansai Region: a prospective community-based cohort (HEIJO-KYO)” study was conducted in 2010-2014 between the months of September and April. We recruited community-dwelling elderly individuals aged ≥60 years with the cooperation of local residents’ associations and elderly residents’ clubs in Nara, Japan. Of 1,127 subjects in the HEIJO-KYO cohort, the ocular status in 661 participants were evaluated. All participants provided written informed consent. The study protocol was approved by the Nara Medical University ethics committee.

Assessment of Cataracts
Ocular status was assessed in photographs of anterior segments obtained using slit lamp biomicroscopy (SL 130, Carl Zeiss Meditec AG, Germany) by a senior ophthalmologist (K.M.) after pupillary dilatation using topical 5% phenylephrine hydrochloride (Kowa Pharmaceutical Co., Ltd, Tokyo, Japan). To avoid acute primary angle closure risk, pupillary dilatation was not performed in participants with a narrow angle. Nuclear sclerosis was assessed using a narrow-slit beam oriented 45° to the line of sight, and cortical and posterior subcapsular opacities were assessed using retroillumination photography. Cataract was graded using the Lens Opacities Classification System III (LOCS III) chart with 0.25-unit intervals by another senior ophthalmologist (T.Y.) who was blinded to the participants’ medical information. Cataract was defined as nuclear cataract grade ≥2.0, cortical cataract grade ≥2.0, or posterior subcapsular cataract grade ≥2.0 in both eyes. The 2 senior ophthalmologists (T.Y. and K.M.) had sufficient agreement in nuclear cataract grading for the initial consecutive 276 eyes.

Measurements of Carotid IMT
To measure carotid IMT, CCA ultrasonography was performed using a 7.5-MHz linear array transducer (Aplo MX/Viamo, Toshiba Medical Systems Corporation, Tokyo, Japan) by 2 trained sonographers without the participants’ information. We acquired optimal longitudinal images of the distal CCA (0–10 mm proximal to bulb widening or 18–8 mm proximal to the flow divider tip). CCA–IMT was measured excluding focal plaques at the proximal edge, mid-point, or distal edge of the distal CCA in the far wall on the right and left sides. Mean carotid IMT was the average of these 6 CCA–IMT measurements and the maximal carotid IMT was the highest value among them. Intersonographer reproducibility was evaluated by the intraclass correlation coefficient (ICC) of the mean carotid IMT in the initial 107 consecutive participants. The ICC of the mean carotid IMT was 0.86 [95% confidence intervals (CI), 0.81–0.91]. Carotid atherosclerosis was defined as maximal carotid IMT ≥1.1 mm.

Measurement of Covariates
Body mass index (BMI) was calculated by dividing body weight with the square of body height (kg/m²). Current smoking status, socioeconomic status, and medication use were evaluated by self-administered questionnaire. Diabetes mellitus was determined on the basis of medical history, current use of antidiabetic therapy, and fasting plasma
glucose and glycated hemoglobin levels. The estimated glomerular filtration rate (eGFR) was calculated per the Japanese Society of Nephrology–Chronic Kidney Disease Practice Guide. Mean daytime systolic blood pressure (SBP) levels were measured at 30-min intervals for 48 h using a validated ambulatory recorder (TM-2430; A&D Co. Ltd., Tokyo, Japan) and a cuff on the non-dominant arm. An actigraph (Actiwatch 2; Respironics Inc., Murrysville, PA, USA) on the non-dominant wrist was used to record physical activity at 1-min intervals for 2 consecutive daytime periods. Sleep disturbances were defined as a Pittsburgh Sleep Quality Index score ≥6 and current use of sleep medications.16 Urinary 6-sulfatoxymelatonin excretion (UME) was measured in urine samples collected overnight to assess melatonin secretion, as previously described.16

### Statistical Analysis

Means were compared between groups using the unpaired t-test, and the chi-square test was used to compare categorical data. Odds ratio (OR) of carotid atherosclerosis association with cataracts was estimated using logistic regression models. Covariance and logistic regression analysis were used to calculate mean and maximal carotid IMT and OR of carotid atherosclerosis association with cataracts, adjusted for the other associated variables (P<0.20) including age (≥70 vs. <70 years), sex, current smoking, antihypertensive medication, daytime SBP (mmHg), eGFR (mL/min/1.73 m²), daytime physical activity (100 counts/min) and UME. CI, confidence interval; IMT, intima-media thickness. Other abbreviations as in Table 1.

### Results

The mean age of the 442 participants was 70.0±6.3 years, and 224 (50.7%) individuals were males. The mean and maximal carotid IMT was 0.86±0.15 mm and 1.07±0.29 mm, respectively. Compared with the group without carotid atherosclerosis (maximal IMT <1.1, n=299), the carotid atherosclerosis group (maximal IMT ≥1.1, n=143) had individuals with significantly older age, more males and current smokers, and lower eGFR and UME (Table 1).

Cataract was detected in 157 participants (35.5%) and the number of nuclear cataracts, cortical cataracts, and posterior subcapsular cataracts was 122 (78.0%), 30 (19.0%), and 5 (3.2%), respectively. Compared with the group without cataracts (n=285), the cataract group (n=157) had individuals with significantly older age, more males and current smokers, and lower eGFR and UME (Table 2).

<table>
<thead>
<tr>
<th>Cataracts</th>
<th>With (n=157)</th>
<th>Without (n=285)</th>
<th>Difference (With–Without, 95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean IMT, mm</td>
<td>0.89 (0.86, 0.91)</td>
<td>0.84 (0.83, 0.86)</td>
<td>0.04 (0.01, 0.07)</td>
<td>0.003</td>
</tr>
<tr>
<td>Maximal IMT, mm</td>
<td>1.12 (1.07, 1.16)</td>
<td>1.04 (1.00, 1.07)</td>
<td>0.08 (0.02, 0.14)</td>
<td>0.006</td>
</tr>
<tr>
<td>Adjusted model 1</td>
<td>0.88 (0.86, 0.91)</td>
<td>0.85 (0.83, 0.86)</td>
<td>0.04 (0.01, 0.07)</td>
<td>0.012</td>
</tr>
<tr>
<td>Maximal IMT, mm</td>
<td>1.11 (1.07, 1.12)</td>
<td>1.04 (1.01, 1.08)</td>
<td>0.07 (0.01, 0.13)</td>
<td>0.018</td>
</tr>
<tr>
<td>Adjusted model 2</td>
<td>0.88 (0.86, 0.90)</td>
<td>0.85 (0.83, 0.86)</td>
<td>0.04 (0.01, 0.06)</td>
<td>0.012</td>
</tr>
<tr>
<td>Maximal IMT, mm</td>
<td>1.11 (1.06, 1.15)</td>
<td>1.04 (1.01, 1.08)</td>
<td>0.07 (0.01, 0.12)</td>
<td>0.021</td>
</tr>
<tr>
<td>Adjusted model 3</td>
<td>0.88 (0.86, 0.90)</td>
<td>0.85 (0.83, 0.86)</td>
<td>0.04 (0.01, 0.06)</td>
<td>0.013</td>
</tr>
<tr>
<td>Maximal IMT, mm</td>
<td>1.11 (1.06, 1.15)</td>
<td>1.04 (1.01, 1.08)</td>
<td>0.06 (0.01, 0.12)</td>
<td>0.027</td>
</tr>
</tbody>
</table>

Model 1: adjusted for age, sex, and smoking. Model 2: adjusted for age, sex, smoking, antihypertensive medication, daytime BP levels, and eGFR. Model 3: adjusted for age, sex, smoking, antihypertensive medication, daytime BP levels, eGFR, daytime physical activity, and UME. OR, odds ratio. Other abbreviations as in Tables 1,2.
terior subcapsular cataracts were 63 (14.3%), 104 (23.5%), and 28 (6.3%), respectively. The mean and maximal carotid IMT was significantly greater in the cataract group (n=157) than in the non- cataract group (n=285), with a mean difference of 0.04 (95% CI, 0.01–0.07) and 0.08 (95% CI, 0.02–0.14), respectively (Table 2). In the multivariable models adjusted for potential confounding factors, including age, sex, smoking, antihypertensive medication, daytime SBP levels, eGFR, daytime physical activity, and UME, the mean and maximal carotid IMT were significantly higher in the cataract group than in the non- cataract group (mean IMT: mean, 1.11 vs. 1.04 mm, respectively; difference, 0.07; 95% CI, 0.01–0.12; P=0.021; maximal IMT: mean, 0.88 vs. 0.85 mm, respectively; difference, 0.04; 95% CI, 0.01–0.07; P=0.012; adjusted model 2). Further adjustment for BMI or diabetes did not change the significance (data not shown).

Carotid atherosclerosis prevalence was significantly higher in the cataract group than in the non- cataract group (40.8 vs. 27.7%, respectively) (Table 3). Logistic regression analysis revealed a significantly higher OR for carotid atherosclerosis in the cataract group than in the non- cataract group (OR, 1.79; 95% CI, 1.19–2.71). In the multivariable models adjusted for potential confounding factors, the cataract group had a higher OR for carotid atherosclerosis than the non- cataract group (adjusted model 2; OR, 1.78; 95% CI, 1.14–2.78; P=0.011; adjusted model 3; OR, 1.77; 95% CI, 1.13–2.77; P=0.012). Sensitivity analysis adjusting for data on 5-year age-categories suggested consistent result (adjusted model 2; OR, 1.64; 95% CI, 1.05–2.57; P=0.032).

Discussion

We found a clear and significant association between cataracts and subclinical carotid atherosclerosis, independent of known risk factors of both cataracts and atherosclerosis including aging, smoking, hypertension, and diabetes. The strength of this study includes the objective assessment of ocular status via slit lamp biomicroscopy and CCA–IMT via ultrasonography in a large general elderly population.

Our observations are consistent with previous epidemiological evidence of increased cardiovascular disease risk, including carotid artery disease, in patients with cataracts; we have provided novel subclinical-level evidence of a significant association between cataracts and carotid atherosclerosis. A Taiwanese nationwide retrospective cohort study suggested a higher prevalence of ischemic heart disease in cataract patients (n=32,456) compared with their propensity score-matched cohort without cataracts (n=32,456). Another study suggested a higher prevalence of carotid artery disease in cataract patients (n=12,984) than in matched controls (n=25,968). Other studies have suggested positive associations between cataracts and cardiovascular disease. A cross-sectional study suggested a significantly thickened CCA–IMT in patients with coexistent cataract and age-related macular degeneration (AMD) (n=47) than in patients with either cataract (n=35) or AMD (n=49); however, it is difficult to interpret those results because of the pathogenetic heterogeneity in cataract and AMD. Our observation included a significantly thickened CCA–IMT in elderly individuals with cataracts (n=157) than in those without (n=285).

Oxidative stress is a major etiological factor in both cataracts and atherosclerosis; recent chronobiological studies suggest a possible pathway of decreased light reception in cataracts leading to potential circadian misalignment, resulting in exacerbation of atherosclerosis. Oxidative stress to proteins and lipids in the lens is an important trigger of cataract formation. In addition, the atherosclerotic process is primarily attributed to chronic inflammation related to oxidative stress in the vasculature. The association between cataract and carotid atherosclerosis observed in the present study may have been affected by uncontrollable confounding effects of oxidative and non-oxidative stress that were not measured, although the multivariable statistical models in the present study included age, smoking, hypertension, diabetes, and renal function.

Thus, the clinical implications of an increase in carotid IMT associated with cataracts and consequent cardiovascular events could be assessed in a population-based prospective study with a 6.2-year follow-up period. A 0.07-mm increase in maximal CCA–IMT in elderly individuals with cataracts corresponded to an increase in myocardial infarction rate by 8.4% and ischemic stroke rate by 9.8%. Further prospective studies are needed to better understand the effects of cataracts on carotid atherosclerosis. In addition, studies investigating the preventive effects of cataract surgery on atherosclerosis in a randomized manner are needed.

Recent advances in chronobiological research suggest the importance of circadian biological rhythms in the atherosclerotic process. Light information is a primary environmental cue to synchronize biological rhythms to environmental conditions. Cataracts drastically decreases light transmission to the retina in early stages, particularly light below the 500 nm wavelength, which is important in circadian physiology, potentially resulting in circadian misalignment and sleep disturbances. Clock gene mutations induce atherosclerosis and altered vascular endothelial function in mice. In humans, circadian misalignment and poor sleep increase catecholamine levels, vascular tone, and sympathetic activity, which play significant roles in atherosclerosis. However, in the present study, the association between cataracts and carotid atherosclerosis was independent of circadian rhythm parameters, such as daytime physical activity and nighttime melatonin levels.

Study Limitations

First, the study had a cross-sectional design and causality cannot be ascertained. Further prospective studies are warranted. Second, the sampling was non-random. The participants were recruited through local residents’ associations and elderly residents’ clubs, and most were excluded because of incomplete ocular assessments or carotid IMT measurements and previous cataract surgery. These may have led to selection bias. However, some basic data including BMI and eGFR were concordant with those in the Japanese national data, and did not significantly differ between the 685 excluded participants and the 442 included participants (data not shown). Third, cataract was graded by a single senior ophthalmologist, which may have resulted in misclassification; however, there was sufficient agreement with another senior ophthalmologist in cataract grading. Fourth,
quantitative analysis on the cataract grades and subtypes could not be conducted because of the relatively small sample size of each cataract grade and subtype.

Conclusions

This study suggested that cataracts may be associated with subclinical carotid atherosclerosis in an elderly population. The association was independent of known risk factors of both cataracts and atherosclerosis, including aging, smoking, hypertension, and diabetes. Further prospective studies are needed to better understand the effects of cataracts on carotid atherosclerosis.

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Conflict of Interest

K.O. and K.S. received research grants from YKK AP Inc.; Ushio Inc.; Tokyo Electric Power Company; EnviroLife Research Institute Co., Ltd.; Sekisui Chemical Co., Ltd.; LIXIL Corp.; and KYOCERA Corp.

References