

Association Between the Asymmetric Dimethylarginine Levels and Glaucoma Severity: A Cross-Sectional Analysis of the LIGHT Study

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PURPOSE. Asymmetric dimethylarginine (ADMA), a potent endogenous inhibitor of nitric oxide synthase, may be involved in the pathophysiology of glaucoma by dysfunctioning nitric oxide and oxidative stress. The purpose of this study was to determine whether the serum ADMA level is associated with the severity of glaucoma.

METHODS. One hundred twenty-five patients with glaucoma (mean age 69.4 years) were analyzed in this cross-sectional study. The severity of glaucoma was determined by the visual field mean deviation in the worse eye; severe, a mean deviation ≤ -12 dB; and mild, a mean deviation > -12 dB. The serum ADMA levels were classified into three groups according to tertiles; low (T1), intermediate (T2), and high group (T3).

RESULTS. The mean serum ADMA levels in the severe glaucoma group was significantly higher than that in the mild glaucoma group (0.41 vs. 0.39 $\mu\text{mol/L}$; $P = 0.031$). A significantly higher prevalence of patients with severe glaucoma was found in the T3 group than that in the T1 group (T1, 44.7% and T3, 68.2%; $P = 0.018$). In the multivariable logistic regression analysis adjusted for the potential confounders, e.g., age, sex, obesity, smoking, hypertension, diabetes, and renal function, the odds ratio for severe glaucoma in the T3 group was significantly higher than that in the T1 group (odds ratio 3.02; 95% confidence interval 1.04 to 8.79; $P = 0.043$).

CONCLUSIONS. A significant association between higher serum ADMA levels and severe glaucoma was found, and this association remained significant after adjusting for the potential confounders.

Keywords: glaucoma, asymmetric dimethylarginine, nitric oxide, oxidative stress, nitric oxide synthase

Glaucoma is a neurodegenerative disease characterized by a progressive loss of retinal ganglion cells and subsequent visual field damages.¹ The mechanical stress induced by an elevation of the intraocular pressure and the ischemic stress induced by the impaired microcirculation in the optic disc have been proposed to be the basis for the pathophysiology of glaucoma.² In addition to these two major mechanisms, epidemiological studies have suggested that several systemic diseases such as chronic kidney disease, hypertension, and diabetes were risk factors for glaucoma.³⁻⁵ However, the underlying mechanisms of how these systemic diseases are involved in the pathophysiology of glaucoma have not been definitively determined.

Asymmetric dimethylarginine (ADMA) is a potent endogenous competitive inhibitor of nitric oxide synthase (NOS).⁶ An increase in the ADMA levels inhibits the nitric oxide (NO) bioactivity, leading to the suppression of the protective effects of NO on endothelial function and vascular tone.⁶ In fact, ADMA is known to be a major cause of endothelial dysfunction⁶ and is an independent risk factor for chronic kidney disease, cardiovascular disease, and all causes of mortality.⁷⁻⁹ In addition, NOS uncoupling caused

by an increase in ADMA levels leads to oxidative stress caused by the production of the reactive oxygen species.⁸

An experimental study has provided evidence that oxidative stress can lead to retinal ganglion cell death,¹⁰ and a clinical study has reported on a significant association between the levels of a systemic oxidative stress markers and glaucomatous visual field damages.¹¹ Additionally, evidence is accumulating that the NO pathway is involved in the regulation of the intraocular pressure and ocular blood flow.¹² Thus ADMA may contribute to the pathophysiology of glaucoma through oxidative stress and inhibition of NO bioactivity. A few clinical studies have shown that the level of ADMA in the serum and aqueous humor of patients with glaucoma was higher than that of the control participants without glaucoma.^{13,14} However, whether the ADMA levels is associated with the severity of the glaucomatous visual field damages remains to be investigated.

The purpose of this cross-sectional study was to determine whether the patients with severe glaucoma had higher serum ADMA levels than that of patients with mild glaucoma. To accomplish this, we measured the serum ADMA levels in 125 patients with primary open-angle glaucoma and

determined whether it was significantly correlated to the severity of glaucoma determined by the visual field mean deviation (MD).

METHODS

Patients With Glaucoma

We studied 125 patients with primary open-angle glaucoma including normal tension glaucoma who had at least one glaucomatous eye and were participants in the LIGHT study. The data from these patients were collected between in May 2017 to December 2019. The LIGHT study, “A Longitudinal study of biological circadian rhythms In Glaucoma patients: Home Testing of circadian intraocular pressure and biological parameters,” was described in detail earlier.¹⁵ The Ethics Committee of Nara Medical University approved the protocol of the LIGHT study (approval number: 1314), and the protocol conformed to the tenets of the Declaration of Helsinki. This protocol was registered with the University Hospital Medical Information Network Clinical Trials Registry (registration number; UMIN000027299). A written informed consent for the LIGHT study was obtained from all patients with glaucoma.

For the diagnosis and severity of glaucoma assessments, all patients with glaucoma had complete ophthalmic evaluations including slit-lamp biomicroscopy, indirect ophthalmoscopy, gonioscopy, best-corrected visual acuity (BCVA), intraocular pressure by Goldmann applanation tonometry, retinal nerve fiber layer thickness measured by spectral-domain optical coherence tomography (Spectralis; Heidelberg Engineering, Heidelberg, Germany), and visual field assessments by standard automated perimetry. The diagnosis of glaucoma was based on the presence of a glaucomatous optic disc and visual field defects determined by one glaucoma specialist (T.Y.) as described in detail.¹⁶ Of the 125 patients with glaucoma, 96 (76.8%) had bilateral glaucoma.

Assessment of Visual Field Examinations

The visual field examinations were determined with the Humphrey Field Analyzer (Humphrey, Carl Zeiss Meditec, Dublin, CA, USA) using the 30-2 Swedish interactive threshold algorithm standard program. The visual field MD was used to determine the diagnosis and the severity of the glaucoma. In case of bilateral glaucoma, the visual field MD of the more severe glaucoma eye was used in the statistical analyses. Mild glaucoma was defined as eyes with a visual field MD > -12 decibel (dB) and severe glaucoma was defined as eyes with a MD ≤ -12 dB. The results of the visual field examinations with false-positive response >15% were excluded based on the findings of an earlier study.¹⁷⁻¹⁹

Measurement of the Serum ADMA Levels

Fasting venous blood samples were collected in the morning for the measurement of the serum ADMA concentration and stored at -80 °C. The serum ADMA concentration was measured by high-performance liquid chromatography by a commercial laboratory (SRL Inc., Tokyo, Japan). The lower ADMA detection limit was 0.1 μmol/L, and all of the samples had ADMA levels over the detection limit. The serum ADMA levels were classified into three tertiles groups; T1 (≤0.37, n = 38), T2 (0.38–0.41, n = 43), and T3 (≥0.42, n = 44).

Other Measurements

Obesity was defined as a body mass index ≥25. The body mass index was calculated by dividing the weight (kg) by height (m²). Smoking was determined by a self-administered questionnaire. Hypertension was defined by the medical history and the use of antihypertension drugs. Diabetes mellitus was defined by a current diabetes treatment or fasting plasma glucose ≥126 mg/dL or glycated hemoglobin level ≥6.5%. Chronic kidney disease was defined as an estimate glomerular filtration rate <60 mL/min per 1.73 m². The estimate glomerular filtration rate was calculated by the formula from the Japanese Society of Nephrology-Chronic kidney disease guide.²⁰ The decimal BCVA was measured with a standard visual acuity chart, and the decimal BCVA converted to logarithm of minimum angle of resolution (LogMAR) units for the statistical analyses. The mean circum-papillary retinal nerve fiber layer thickness in the global region was used for the statistical analyses. The axial length of the eyes was measured by a partial coherence laser interferometry (IOL master; Carl Zeiss Meditec). The central corneal thickness was measured by a rotating Scheimpflug camera (Pentacam; Oculus, Wetzlar, Germany). The use of topical medications for glaucoma were determined by the medical records and a self-administered questionnaire.

Statistical Analyses

Variables with a normal distribution were presented as the means ± standard deviation (SD) and analyzed by unpaired t tests. Categorical data were analyzed by χ^2 tests. Trend analyses for the tertiles of the serum ADMA levels with means and proportions were performed by using linear and logistic regression models for significant trends. The odds ratio (OR) and 95% confidence interval (CI) for severe glaucoma were calculated by using multivariable logistic regression model. Potential confounders of the multivariable model were considered to be basic parameters, for example, age, sex, obesity, and smoking, and the clinical parameters such as hypertension, diabetes, and chronic kidney disease (Table 1). The adjusted mean difference of serum ADMA levels among the three glaucoma groups was assessed by analysis of covariance. All of the data were analyzed with SPSS version 25 (IBM SPSS Statistics, Inc, Chicago, IL, USA). A two-side *P* value <0.05 was considered statistically significant.

RESULTS

The mean ± SD age was 68.3 ± 12.0 years for the 61 mild glaucoma patients and 70.5 ± 10.4 years for the 64 severe glaucoma patients. The prevalence of male in the severe glaucoma group was significantly higher than that in the mild glaucoma group. No significant association was found between the severity of glaucoma and any of the basic and clinical parameters except for the prevalence of male. Higher serum ADMA levels was significantly associated with older age, higher prevalence of hypertension, and chronic kidney disease (*P* < 0.001, *P* = 0.004, and *P* = 0.021, respectively; Table 1).

The mean ± SD of the serum ADMA levels in all patients was 0.40 ± 0.06 with a range of 0.27 to 0.59 μmol/L (Supplementary Fig. S1). The serum ADMA levels in the severe glaucoma group was 0.41 μmol/L, which was significantly higher than that in the mild glaucoma group at 0.39 μmol/L

TABLE 1. Basic and Clinical Parameters By the Severity of Glaucoma and Tertiles of the Serum Asymmetric Dimethylarginine Levels

	Glaucoma			Tertiles of ADMA Levels, $\mu\text{mol/L}$			
	Mild (MD > -12 dB)	Severe (MD \leq -12 dB)	<i>P</i> Value	T1 (≤ 0.37)	T2 (0.38–0.41)	T3 (≥ 0.42)	<i>P</i> for Trend
Number of the patients	61	64		38	43	44	
Basic parameters							
Age, mean (SD), year	68.3 (12.0)	70.5 (10.4)	0.25	63.8 (11.8)	69.9 (10.8)	73.8 (9.0)	<0.001
Sex, male (%)	22 (36.1)	40 (62.5)	0.003	20 (52.6)	18 (41.9)	24 (54.5)	0.82
Obesity, number (%)	15 (24.6)	13 (20.3)	0.57	7 (18.4)	7 (16.3)	14 (31.8)	0.14
Smoking, number (%)	4 (6.6)	7 (10.9)	0.39	3 (7.9)	4 (9.3)	4 (9.1)	0.85
Clinical parameters							
Hypertension, number (%)	16 (26.2)	23 (35.9)	0.24	5 (13.2)	15 (34.9)	19 (43.2)	0.004
Diabetes, number (%)	12 (19.7)	12 (18.8)	0.90	6 (15.8)	7 (16.3)	11 (25.0)	0.28
Chronic kidney disease, number (%)	19 (31.1)	24 (37.5)	0.46	7 (18.4)	17 (39.5)	19 (43.2)	0.021

ADMA, asymmetric dimethylarginine; dB, decibel; MD, mean deviation.

TABLE 2. Logistic Regression Analysis for the Association Between the Severe Glaucoma and the Tertiles of the Serum Asymmetric Dimethylarginine Levels

Variables	Odds Ratio for the Severe Glaucoma (MD \leq -12 dB)					
	Crude Model			Fully Adjusted Model		
	Odds Ratio	95% CI	<i>P</i> Value	Odds Ratio	95% CI	<i>P</i> Value
Tertiles of the serum ADMA levels						
T2 vs T1 (ref)	0.80	0.33, 1.96	0.64	0.84	0.31, 2.23	0.72
T3 vs T1 (ref)	2.65	1.08, 6.52	0.034	3.02	1.04, 8.79	0.043
Age (per year)	1.02	0.99, 1.05	0.25	1.003	0.97, 1.04	0.89
Sex (male vs female)	2.96	1.43, 6.12	0.004	3.43	1.49, 7.91	0.004
Obesity (yes vs no)	0.78	0.34, 1.82	0.57	0.44	0.16, 1.21	0.11
Smoking (yes vs no)	1.75	0.49, 6.31	0.39	1.55	0.34, 7.00	0.57
Hypertension (yes vs no)	1.58	0.73, 3.39	0.24	1.31	0.53, 3.25	0.56
Diabetes (yes vs no)	0.94	0.39, 2.30	0.90	0.73	0.25, 2.09	0.56
Chronic kidney disease (yes vs no)	1.33	0.63, 2.78	0.46	0.96	0.41, 2.25	0.93

ADMA, asymmetric dimethylarginine; CI, confidence interval.

($P = 0.031$). Severe glaucoma group was significantly associated with poor visual acuity and a thinner circumpapillary retinal nerve fiber layer thickness compared to the mild glaucoma group ($P = 0.003$ and $P < 0.001$, respectively). The prevalence of eyes treated by topical medications of prostaglandin, beta blocker, and carbonic anhydrase inhibitor in the severe glaucoma was significantly higher than that in the mild glaucoma (all $P < 0.001$; Supplementary Table S1).

The number of the patients with severe glaucoma (MD \leq -12 dB) in the low (T1), intermediate (T2), and high ADMA group (T3) was 17 (44.7%), 17 (39.5%), and 30 (68.2%), respectively. The prevalence of patients with severe glaucoma in the high ADMA (T3) group was significantly higher than that in the low ADMA (T1) group ($P = 0.018$). In the analyses of the association between the severe glaucoma and the serum ADMA tertiles group (Table 2), univariable logistic regression analysis showed a significantly higher OR for the severe glaucoma in the high ADMA (T3) group compared to that in the low ADMA (T1) group (OR, 2.65; 95% CI, 1.08–6.52; $P = 0.034$). Similarly, the OR for the severe glaucoma was significantly higher in relation to 0.1 $\mu\text{mol/L}$ of the serum ADMA levels (OR, 1.99; 95% CI, 1.05 to 3.78; $P = 0.035$). In the multivariable logistic regression model adjusted for potential confounders including age, sex, obesity, smoking, hypertension, diabetes, and chronic kidney disease, the OR for the severe glaucoma in the high

ADMA (T3) group was significantly higher than that in the low ADMA (T1) group (OR, 3.02; 95% CI, 1.04–8.79; $P = 0.043$; Table 2).

In further analyses of the three glaucoma groups (early: MD \geq -6 dB; moderate: -6 dB > MD > -12 dB; and severe: MD \leq -12 dB), the mean serum ADMA levels in the early, moderate, and severe groups were 0.38, 0.40, and 0.41 $\mu\text{mol/L}$, respectively. The serum ADMA levels in the severe glaucoma group was significantly higher than that in the early glaucoma group (age-adjusted model: mean difference, 0.03; 95% CI, 0.004–0.05; $P = 0.025$). No significant association was found between the early and moderate glaucoma group for the serum ADMA levels ($P = 0.20$).

DISCUSSION

This cross-sectional study of 125 glaucoma patients was designed to determine the significance of the association between the severity of glaucoma and the serum ADMA levels. The novel results showed that higher ADMA levels were significantly associated with the patients with severe glaucoma independent of the important potential confounders including age, hypertension, diabetes and renal function. The strength of this study was the large sample size of 125 glaucoma patients from a hospital based-cohort, and the adjustments of the confounding factors for glaucoma and ADMA.

At present, the association of ADMA levels and glaucoma is somewhat controversial mainly because of the limited number of the previous studies.^{13,14,21,22} The earlier study with the largest sample size of 211 patients with advanced glaucoma and 295 participants without glaucoma reported that the serum ADMA levels in advanced glaucoma were significantly higher than that of the control participants.¹³ Our findings are consistent with the results of this previous study. However, that study had several limitations. First, it was unclear whether the serum ADMA levels were related to the glaucomatous visual field damages because only advanced-stage glaucoma patients were studied. Second, although chronic kidney disease, hypertension, and diabetes are recognized to be confounding factors for both glaucoma and serum ADMA levels,^{3-5,7} the authors did not include these variables in their statistical analyses.¹³ To the best of our knowledge, our findings are the first study in which the serum ADMA levels were significantly associated with the severity of glaucoma independent of these potential confounding factors.

High ADMA levels may contribute to the pathophysiology of glaucoma by two mechanisms: inhibition of the NO bioactivity and by an increase of oxidative stress. First, ADMA can inhibit the beneficial effects of NO on systemic functions such as endothelial function, vasodilation, and regulation of blood pressure.⁸ NO is a signaling molecule produced from L-arginine by NOS and is a therapeutic target for glaucoma through the NO-guanylate cyclase pathway.¹² The results of an experimental study showed that administration of a NO donor directory decreased the intraocular pressure through alterations of the function of the trabecular meshwork and Schlemm's canal.^{12,23} In addition, the protective effects of NO on autoregulation in the optic nerve head have been reported in an experimental study on rabbits with elevated intraocular pressure.²⁴ Second, ADMA is involved in NOS uncoupling and the subsequent production of reactive oxygen species such as superoxide production, possibly leading to the loss of retinal ganglion cells through oxidative stress.⁸ Several clinical studies and a meta-analysis study reported that an increase in oxidative stress markers such as 8-hydroxy-2-deoxyguanosine, a representative marker for oxidative DNA damage in human trabecular meshwork, is present in the serum and aqueous humor of patients with glaucoma.²⁵⁻²⁷ Also, an antioxidative stress factor, NF-E2-related factor 2, can prevented the effects of nerve crush on retinal ganglion cells death.¹⁰

ADMA may be an important mediator that links several systemic diseases, such as chronic kidney disease, hypertension, and diabetes, to glaucoma. ADMA is produced by the proteolysis of posttranslational methylated proteins and is eliminated partly by urine excretion and mainly degradation by dimethylarginine dimethylaminohydrolase (DDAH). The ADMA levels is elevated in patients with renal dysfunction, cardiovascular disease, and diabetes.²⁸⁻³⁰ The mechanisms causing the increased ADMA levels in patients with these systemic diseases are proposed to be an increase in the production of ADMA (turnover of protein containing methylated arginine in response to stress) and a decrease in elimination of ADMA (decrease in renal excretion and degradation by dysfunction of DDAH).⁸ In fact, the impairments of DDAH activity in diabetic model rats have been shown to be correlated with an elevation of the ADMA levels.³¹ Thus the linkage of these systemic diseases to pathophysiology of glaucoma may be mediated through elevation of the ADMA levels.

Our results indicated that the serum ADMA levels may be a potential predictor of a progression of glaucoma. In fact, ADMA is known to be an important predictive marker for the progression of the chronic kidney disease, mortality, and cardiovascular diseases.^{32,33} A meta-analysis study demonstrated that higher ADMA levels by 0.1 $\mu\text{mol/L}$ had a 7% and 5% increased risk for all-cause mortality and cardiovascular diseases, respectively.³³ However, the design of our study was a cross-sectional and whether the serum ADMA levels can predict the progression of glaucoma was not determined. Further longitudinal studies of the serum ADMA levels and progression of glaucoma are needed.

There are several limitations in this study. First, the study participants were not randomly selected, which could possibly lead to selection bias. Second, the NO levels and oxidative stress markers in the participants were not measured. Third, it is unclear whether the serum ADMA levels of our glaucoma patients were within the normal range because of a lack of a control group. Although the earlier meta-analysis study reported that the reference range of ADMA levels (95% CI) measured by high-performance liquid chromatography was 0.34 (0.29–0.38) to 1.10 (0.85–1.35) $\mu\text{mol/L}$ in healthy participants,³⁴ the reference range of ADMA levels has not been definitively determined because of influence of race differences and age. Fourth, the influence of the treatment for glaucoma on the serum ADMA levels is unclear. Systemic beta blockers have been shown to affect serum ADMA levels.³⁵ Topical medications for glaucoma may also lead to alteration in the serum and aqueous humor ADMA levels.

In conclusion, the results of 125 patients with glaucoma revealed that the higher serum ADMA levels were associated with severe glaucoma. This association was independent of the confounding factors.

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