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ORIGINAL RESEARCH

Serum free fatty acids levels not associated with normal tension glaucoma

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Purpose: To determine the free fatty acid levels in the sera of patients with normal-tension glaucoma and compare it with that of normal controls.

Methods: Forty-four consecutive patients with newly diagnosed normal-tension glaucoma and forty-four age and gender matched controls were evaluated. The type and level of fatty acids in the sera were measured by gas chromatography (Model GC17A; Shimazu, Kyoto, Japan). Twenty-four fatty acids were identified from 12:0 to 24:1. The values were compared between the normal-tension glaucoma and control groups by Mann–Whitney *U* tests.

Results: No statistically significant difference was found in the levels of any free fatty acids between the normal-tension glaucoma group and control group.

Conclusion: No significant association was found in the serum free fatty acids levels including docosahexaenoic acid and eicosapentaenoic acid between normal-tension glaucoma patients and controls.

Keywords: free fatty acid, docosahexaenoic acid, eicosapentaenoic acid, normal tension glaucoma

Introduction

Glaucoma is the second leading cause of blindness in the world, affecting 700 million people, and is the leading cause of blindness in Japan affecting four million people.[1] Elevated intraocular pressure (IOP) is a major risk factor for the progression of glaucomatous optic neuropathy.[2,3] However, the 24-hour IOPs of some patients remain within the normal range, the so-called normal-tension glaucoma (NTG) patients. In Japan, in 92% of patients with primary open-angle glaucoma (POAG), the IOP was 21 mm Hg or less.[1]

The n-3 and n-6 polyunsaturated free fatty acids (PUFAs) are essential nutrients, but cannot be synthesized by mammalians and have to be ingested in the diet. The PUFAs, including docosahexaenoic acid (DHA), α-linolenic acid, and eicosapentanoic acid (EPA) have been shown to have neuroprotective and anti-inflammatory actions, and are implicated in the pathogenesis of some degenerative retinal diseases and neurodegerative disease.[4–7] Kang and colleagues showed there was a positive association between the dietary intake of the n-3 to n-6 polyunsaturated fat dietary intake and the risk of POAG. This association was stronger for patients with high-tension POAG.[8]

Relevant to NTG, Shimazawa and colleagues showed that DHA has neuroprotective effects against oxidative stress in retinal ganglion cells *in vitro*.[9] Nguyen and colleagues reported that a n-3 deficient diet induced a significant decrease (–27.4%) in the scotopic threshold response of the electroretinogram which represents the activity of the retinal ganglion cells.[10]

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We hypothesized that a decrease in the level of serum n-3 causes ganglion cell dysfunction and is the cause of clinical manifestations, namely, optic disc cupping, glaucomatous visual field defects, in patients with normal tension glaucoma. To test this hypothesis, we measured the level of n-3 and n-6 PUFAs in the serum of patients with NTG and compared it to the level in normal healthy controls.

Methods

Forty-four consecutive patients (20 men, 24 women; average age ± standard deviation, 59.9 ± 9.8 years) with newly diagnosed NTG who came to the Glaucoma Clinic of Keio University Hospital from January 2005 to May 2007 were studied. The procedures used conformed to the Tenets of the Declaration of Helsinki. A written informed consent was obtained from all subjects. This study was approved by the Ethics Committee of the Keio University School of Medicine. All subjects underwent a complete ophthalmological examination including best-corrected visual acuity, slit-lamp biomicroscopy, pentacam corneal thickness evaluation (Oculus Inc, Wetzlar, Germany), Goldmann applanation tonometry, gonioscopy, funduscopy, and optic disc evaluation with a 90-diopter lens by a single investigator (KY) with subspecialty training in glaucoma. In addition, perimetry was performed with a Humphrey field analysis using the 30-2 Swedish Interactive Threshold Algorithm Standard Strategy (Carl Zeiss Meditec, Dublin, CA, USA).

The diagnostic criteria for NTG were; open anterior chamber angles on gonioscopy, glaucomatous optic disc cupping (cup-to disc ratio >0.7 with thinning or notching of the neural rim), and characteristic optic nerve-related visual field loss on Humphrey perimetry. All criteria were confirmed by at least a second visual field examination. Reliability was <20% fixation losses, <33% false-positive results, and <33% false negative results.

The diurnal IOP measurements was performed seven times at 6:00, 9:00, 12:00, 15:00, 18:00, 21:00, and 24:00 hours. In all patients, the IOPs were <21 mm Hg. Seven patients were excluded because the highest diurnal IOP was >21 mm Hg. To eliminate the effect of central corneal thickness on the IOP, we re-calculated the IOP of the NTG patients by the following equation: corrected IOP = IOP reading –0.012 × (CCT in μm-520).[11] The IOP of all the NTG patients was <21 mm Hg after the correction.

Subjects with other ophthalmic conditions such as angle closure glaucoma, pigment dispersion glaucoma, exfoliative glaucoma, trauma, any other type of secondary glaucoma, subjects aged below 40 or over 85 years, were excluded. None of the patients and controls had been taking vitamins, steroids, and had ever smoked.

The control subjects were recruited from patients who came to the clinic for annual ophthalmic check-up from January 2005 to May 2007. The 44 control subjects (16 men, 28 women; average age ± standard deviation: 62.7 ± 14.8 years) did not have any history of ocular diseases, and underwent the same examinations as the patients by the same investigator. Humphrey visual field testing and central corneal thickness measurements were not performed in the control group because ocular examination results were normal.

Blood sampling

Fasting blood after 12 hours was collected from the forearm vein of all of the patients and controls in 5-ml tubes before noon. The blood samples were then centrifuged at 3000 *g* for 10 minutes and stored at –80°C before the analyses.

Fatty acids were measured with a gas chromatograph (Model GC17A; Shimazu, Kyoto, Japan). A total of 24 fatty acids were identified from 12:0 to 24:1. The serum level of each fatty acid was expressed in μg/ml, and the ratio of n-3 to n-6 polyunsaturated fatty acids was calculated.

Statistical analyses

The age and IOP were compared between NTG and control groups by unpaired *t*-tests. Gender, prevalence of diabetes mellitus, and hypertension were compared between NTG and control groups by the Fisher's exact test. The data between NTG and control groups were compared with Mann–Whitney *U* test. We also calculated the correlation between the IOP

Table 1 Demographics of the NTG and control group. Data are expressed as mean ± standard deviation

Demographics	NTG (n = 44)	Control (n = 44)	*P* value
Age (years)	59.9 ± 9.8	62.7 ± 14.8	0.19
Men/women	20/24	16/28	0.85
IOP right eye (mm Hg)	16.0 ± 2.3	13.6 ± 2.5	0.001
IOP left eye (mm Hg)	15.7 ± 2.5	14.2 ± 2.7	0.001
Mean deviation right eye (dB)	–6.3 ± 7.8		
Mean deviation left eye (dB)	–6.2 ± 7.5		
CCT right eye (μm)	526.5 ± 29.1		
CCT left eye (μm)	523.9 ± 28.7		
DM	4 (9.0%)	4 (9.0%)	0.92
HT	7 (15.9%)	2 (4.5%)	0.10

Notes: The IOP in Table 1 was not adjusted by calculation.
Abbreviations: NTG, normal-tension glaucoma; IOP, intraocular pressure; CCT, central corneal thickness; DM, diabetes mellitus; HT, hypertension.

and the PUFAs by Pearson product-moment correlation coefficient. A *P*-value less than 0.05 was considered statistically significant. Statistical analyses were performed with the SPSS statistical package for Windows (v. 15.00 SPSS Inc, Chicago, IL, USA).

Results

The clinical characteristics of the NTG patients and control subjects are shown in Table 1. No significant difference was found between the two groups in age, gender, and prevalence of diabetes mellitus and hypertension. The mean IOP was significantly higher in NTG patients than in normal controls.

The level of serum free fatty acids and the ratio of n-3 to n-6 polyunsaturated fatty acid level were not statistically different between NTG patients and healthy controls (Table 2).

No significant correlation was found between IOP and the level of each free fatty acid or the n-3/n-6 ratio in the normal control.

Discussion

Our findings showed that the serum levels of the free fatty acid in the patients with NTG did not differ significantly from that in the normal controls. We could not find any significant correlation between NTG and the free fatty acid levels including EPA and DHA, which had been reported to be lower in POAG patients.[12] The discrepancy of our results to those reported may be because the subjects of the earlier study were patients with POAG whose mean IOP was about 40 mm Hg, and our subjects had NTG with a mean IOP was in the normal range. The IOP depends on a balance in the production of aqueous humor by the ciliary body and the outflow through

Table 2 Proportional concentrations of fatty acids in serum free fatty acid in NTG patients and healthy controls (μg/mL) and the ratio of n-3 to n-6 polyunsaturated fatty acids. No significant difference was shown in any fatty acids and the ratio of n-3 to n-6 long chain polyunsaturated fatty acids

Fatty acids numerical symbol	Common name	*n-x*	NTG group (n = 44)		Control group (n = 44)		*P* value
			Mean	SD	Mean	SD	
12:0	Lauric acid		3.0	3.1	4.0	4.6	0.63
14:0	Myristic acid		33.8	18.9	37.4	23.9	0.65
14:1	Myristoleic acid	n-5	0.0	0.0	0.0	0.0	1.00
16:0	Palmitic acid		783.9	254.2	764.5	259.0	0.92
16:1	Palmitoleic acid	n-7	63.7	29.0	65.7	31.8	0.67
18:0	Stearic acid		244.7	72.4	243.8	62.6	0.88
18:1	Oleic acid	n-9	656.6	305.8	617.7	216.1	0.98
18:2	Linoleic acid	n-6	923.1	231.5	900.5	177.7	0.83
18:3 (6,9,12)	Gamma-linolenic acid	n-6	10.5	6.0	10.2	5.4	0.91
18:3 (9,12,15)	Alpha-linolenic acid	n-3	29.3	15.1	27.7	12.9	0.47
20:0	Arachidic acid		8.3	2.4	8.4	1.9	0.40
20:1	Eicosenoic acid	n-11	5.5	3.3	5.8	2.7	0.15
20:2	Eicosadienoic acid	n-6	6.6	1.9	6.5	1.8	0.89
20:3 (5,8,11)	Mead acid	n-9	2.1	1.4	1.9	1.0	0.91
20:3 (8,11,14)	Dihomo-gamma-linolenic acid	n-6	31.5	11.8	33.8	12.0	0.35
20:4	Arachidonic acid	n-6	171.1	48.6	167.2	43.9	0.90
20:5	Eicosapetaenoic acid	n-3	96.4	46.7	94.6	59.1	0.55
22:0	Behenic acid		18.5	3.9	18.9	3.9	0.95
22:1	Erucic acid	n-9	1.6	0.7	1.7	0.8	0.85
22:4	Adrenic acid	n-6	4.2	1.7	4.1	1.5	0.72
22:5	Osbond acid	n-6	25.0	9.9	22.9	9.3	0.22
24:0	Lignoceric acid		16.6	3.5	16.6	3.3	0.66
22:6	Docosahexaenoic acid	n-3	162.0	54.9	151.2	56.1	0.34
24:1	Nervonic acid	n-9	36.8	8.3	37.9	9.1	0.31
n-3/n-6			0.29	0.11	0.28	0.12	0.65

Abbreviations: NTG, normal-tension glaucoma; SD, standard deviation.

the trabecular meshwork. Evidence has been accumulating that the change in eyes with glaucoma are associated with oxidative stress. Nguyen and colleagues reported that increasing dietary n-3 reduces IOP with increasing age because of an increase in the outflow facility.[13] Oxidative stress on the cells in the trabecular meshwork can lead to cellular dysfunction which then results in an elevation of the IOP. n-3 fatty acids, such as DHA and EPA, act as antioxidants, so reduction of the levels of DHA and EPA can cause oxidative changes in the cells in trabecular meshwork. This can then result in an IOP elevation.

There are limitations of our study. First, the small sample size, cross-sectional study design, and the large standard deviation observed for the fats make the conclusions less strong. Second, the serum fatty acid composition is influenced by diet, and a dietary survey of patients and controls was not done. However, all of the NTG patients were newly diagnosed, so that the possibility of changing their diet may be relatively low. Therefore, a causal relationship has yet to be established in a large prospective study.

In conclusion, the level of free fatty acids in the sera of the patients with NTG did not differ significantly from that in the controls.

Disclosures

The authors report no conflicts of interest in this work.

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