RESEARCH ARTICLE

Adiponectin and Endothelin-1 are Correlated with the Development of Normal-tension Glaucoma in Metabolic Syndrome Patients

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Abstract

BACKGROUND: Glaucoma can lead to irreversible blindness, but normotension glaucoma (NTG) often shows no early symptoms. However, to date, there is limited knowledge regarding the potential parameters for early detection. Therefore, in this study, various metabolic parameters and biomarkers which may contribute to NTG in metabolic syndrome (MetS) patients were evaluated.

METHODS: A retrospective cross-sectional study was conducted in the National Cardiac Center Harapan Kita Hospital. Mets were confirmed following the IDF criteria. NTG was determined based on normal intraocular pressure (IOP) with a mean defect (MD) of the visual field, thinning of the retinal nerve fiber layer (RNFL), and enlargement of cup disc ratio (CDR) by ocular coherence tomography (OCT). Metabolic parameters results of waist circumference (WC), body weight, body height, body mass index (BMI), blood pressures, HbA1c, fasting blood glucose (FBG), lipid profiles; and biomarkers including thiobarbituric acid reactive substance (TBARS) and ferric reducing antioxidant power (FRAP), leptin, adiponectin, high-sensitivity C-reactive protein (hs-CRP), and endothelin-1 (ET-1) were analyzed. Statistical analysis was performed using comparative and correlative tests.

RESULTS: From 29 subjects, 19 subjects (65.5%) were included in the NTG group and 10 subjects (34.5%) were included in the non-NTG group. In the NTG group, we found significant correlation between MD with systolic blood pressure (p=0.035); CDR with ET-1 (p=0.049); and CDR with adiponectin (p=0.010). The non-NTG group had a significant correlation between MD with BMI (p=0.043); CDR with LDL (p=0.042); and CDR with TG (p=0.031).

CONCLUSION: There are correlation between adiponectin and ET-1 with NTG in MetS patients. Therefore, they might be considered as potential early detectors for NTG in MetS patients.

KEYWORDS: normal tension glaucoma, metabolic syndrome, biomarker, endothelin-1, adiponectin

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Introduction

The aging population in Indonesia keep increasing the past few years (1), and in 2022, the number of elderly reached 10.48% of Indonesia's total population (2). The increase of aging population is aligning with a shift in the epidemiological transition, which usually related with the vision impairment and blindness. Glaucoma is one of the five leading causes of vision impairment and blindness

worldwide, characterized by significant damage of retinal ganglion cells (RGC) and optic nerve degeneration, thinning of the retinal nerve fiber layer (RNFL), and cupping of the optic disc, which lead to irreversible vision loss. In Asia, the prevalence of glaucoma was approximately 3.54%, and the majority were primary open-angle glaucoma (POAG). Most POAG was normal-tension glaucoma (NTG).(3,4)

NTG results from a complex interaction involving several ocular and systemic factors, characterized by glaucomatous optic neuropathy with intra-ocular pressure (IOP) within the normal range. The impact of NTG varies from non-progressive, asymptomatic, to blindness, which reduces productivity and quality of life. There are often no apparent symptoms in the early stage of glaucoma, especially NTG, that make patients unaware of their conditions.(5)

Some biomolecular studies indicated the intertwining of oxidative stress, inflammation, and metabolic syndrome (MetS) with glaucoma. Accordingly, IOP examination alone cannot be used as a basis for predicting the occurrence of glaucoma. IOP values of less than 21 mmHg are regarded as normal, therefore, patients with NTG are often detected later in the disease after the patient experiences a significant visual loss.(3,4) While the proportion of NTG is much greater than non-NTG, there is a limited knowledge on the parameters for early detection to prevent blindness among patients with a history of MetS. Thus, it is necessary to identify the parameters that can be used as biomarkers for NTG. In this study, we measured endothelin-1 (ET-1) as a parameter of endothelial vascular dysfunction; thiobarbituric acid reactive substance (TBARS) and ferric reducing antioxidant power (FRAP) as the parameters to measure oxidative stress level and antioxidant activity; high-sensitivity C-reactive protein (hs-CRP) as an inflammatory marker; as well as adiponectin and leptin as metabolic markers. These parameters were indentified silmutanously to facilitate the early detection and effective treatment of glaucoma as early detection and timely treatment that might avert blindness in NTG cases.

Methods

Study Design and Subjects Recruitment

This retrospective cross-sectional study was conducted at the National Cardiovascular Center Harapan Kita in 2018. Subjects were out-clinic patients, aged ≥40 years old with complete ocular, metabolic and biomarker test results.(6) Subjects with abnormalities in refractory media, retinal, macula, and optic neuropathy were excluded from the study. Based on the calculation of cross-sectional sample size (7), with the prevalence of glaucoma at 3.54% and absolute error at 0.067, the minimal sample size required was 29 study subjects. The protocol of this study was approved by the Research Ethics Committee at the National Cardiovascular Center Harapan Kita (No. LB.02.01/VII/287/KEP.054/2018).

Ocular Parameters Examinations

NTG was determined based on IOP of <21 mmHg; peripapillary RNFL thinning; and increased cup disc ratio (CDR) or asymmetry of cupping between the two eyes of more than 0.2.(8) IOP was measured with tonometer (ICare Pro®, ICare Findland Oy, Fantaa, Findland) which was conducted in the sitting position, and both eyes were anesthetized to prevent bias. Mean deviation (MD) in the visual field loss was measured with a perimeter (Zeiss HFA 3 Type 860®, Flextronics Manufacturing, Singapore). The RNFL was measured with the Optical Coherence Tomography (OCT) (CIRRUS HD OCT 5000®, Flextronics Manufacturing), in which the optimal pupillary alignment, fundus focus, centration of the optic disc, and illumination were ensured before each scan was taken. Fundal cup-to-disc ratio (CDR) was measured with indirect funduscopy (Wide Lens Super Field 90D-Volk®, Volk Optical, Mentor, OH, USA) to examine the posterior segment of eyes. In cases in which both eyes were affected, one eye was randomly selected, and in the control group, the right eye is selected from all cases.

Metabolic Parameters Examinations

All MetS test results used for this study were waist circumference (WC), body weight, body height, body mass index (BMI), systolic blood pressure (SBP), diastolic blood pressure (DBP) HbA1c, fasting blood glucose (FBG), total cholesterol, triglyceride (TG), high-density lipoprotein (HDL), and low-density lipoprotein (LDL). MetS diagnosis was performed based on the 2005 International Diabetes Federation (IDF) guideline with slight modification. MetS was characterized as central obesity with two additional criteria out of four criteria. Central obesity was defined as a WC of >90 cm for males and >80 cm for females. Meanwhile the other four criteria were: elevated SBP of >130 mmHg or under anti-hypertensive drug therapy; FBG of >100 mg/dL or currently treated with an anti-diabetic agent; TG of >150 mg/dL or receiving anti-dyslipidemic therapy; and HDL of <40 mg/dL.(9)

For HbA1c, FBG, total cholesterol, TG, HDL, and LDL test results, previously 10 mL venous blood were drawn from the 8-12 hours fasted subjects. The blood

was processed for HbA1c analysis using a Quo-Test® HbA1c Analyzer (EKF-Diagnostic GmbH, Magdeburg, Germany), as well as for FBG and lipid profile analysis using Cholestech LDX® Analyzer (Abbott-Diagnostics, Shanghai, China).

Biomarkers Examinations

Biomarker test results used for this study were TBARS as lipid peroxidase biomarker, FRAP as oxidative stress protein biomarker, hs-CRP as inflammatory biomarker, endothelin-1 (ET-1) as early endothelial dysfunction biomarker, as well as leptin and adiponectin as metabolic dysregomeric biomarkers. Previously, the 10 mL venous blood drawn for metabolic parameters examinations were also used for the examinations of these biomarkers. TBARS was measured using TBARS/MDA Universal Colorimetric Detection Kit (Arbor Assay, Ann Arbor, MI, USA), FRAP was measured using FRAP™ Detection Kit (Arbor Assay), hs-CRP, ET-1, leptin and adiponectin were measured using Multiskan® Sky Microplate Spectrophotometer with Enzyme Linkes Immunosorbent Assay (ELISA) reader (Thermo Fisher Scientific, Waltham, MA, USA), that operated on a monochromator.

Results

Based on the data obtained, 19 subjects were included in the NTG group and 10 subjects were included in the non-NTG group (Table 1). There was no significant difference in the characteristics of subjects (age, sex, and MetS) between the two groups.

There was no significant difference in metabolic parameters and biomarkers between the NTG and non-NTG groups. However, some significant differences between the two groups were found in the ocular parameters, which were RNFL and CDR (Table 2).

Correlation analysis between parameters were also performed. There were significant correlations between components of ocular parameters, metabolic parameters and biomarkers after stratified by group. Most parameters were correlated and the correlations were positive at $\alpha<0.05$ (Table 3).

Figure 1 showed an example of an OCT result obtained from the study, which include the data of RNFL thickness map, RNFL deviation map, the extracted horizontal tomogram, the extracted vertical tomogram, and RNFL circular tomogram of both right eye/oculus dexter (OD) and left eye/oculus sinister (OS). This example showed that thinning of RFNL affected both eyes, though the left eye had a thinner average RNFL than the right eye, which was indicated in red RNFL symmetry between eyes was 37%. CDR over 0.50 in both eyes suggested disc cupping and possible glaucoma (Figure 1A). The enlarged image of the left eye from the Cirrus OCT RNFL deviation map highlighted the disc margins and a 0.06 mm measurement ring, with yellow and red areas showing reduced thickness compared to the reference dataset (Figure 1B).

Table 1. Characteristics of study subjects.

Characteristics	NTG (n=19)	Non-NTG (n=10)	*p* -value
Age, mean±SD	51.7±5.2	52.5±3.9	0.663[a]
Sex, n (%)			
Male	7 (36.8%)	3 (30.0%)	0.713[b]
Female	12 (63.2%)	7 (70.0%)	
MetS, n (%)			
No	8 (42.1%)	6 (60.0%)	0.359[b]
Yes	11 (57.9%)	4 (40.0%)	

[a]Tested with two independent samples t-test; [b]Tested with Phi coefficient test. Significant if *p*-value<0.05.

Discussion

In current study, there are significant differences between NTG and non-NTG in some ocular parameters, which were MD, RNFL, and CDR. NTG is a subset of POAG, characterized by progressive glaucomatous optic neuropathy and corresponding visual field defects, but with a standard range of IOP.(3) In contrast to NTG, the electrophysiological findings showed that non-NTG had impaired RGC, axons, and visual cortex due to high intraocular pressure.(10) It was reported that in the early stage of NTG, MD was more prominent in the paracentral and peripheral arcuate of the superior hemifield than their corresponding regions in the inferior hemifield.(11) In addition, NTG showed that the field loss was near the center of fixation, while in non-NTG the field loss was more diffuse.(12) Up to 30% to 50% of RGC might be lost before typical visual field testing detected any deficiencies, even in the presence of distinctive visual field impairments that could validate the diagnosis. OCT has made it easier to detect disease early on and to track the gradual loss of optic nerve fibers over time.(13)

The results of this study indicated that the component of metabolic parameters and biomarkers were correlated with the development of NTG and non-NTG. NTG is a result

Table 2. Comparison of ocular parameters, metabolic parameters, and biomarkers in NTG and non-NTG subjects.

Parameters	NTG (n=19)	Non-NTG (n=10)	*p*-value
Ocular parameters			
IOP	14.9±2.8	15.9±2.3	0.399[a]
MD	7.7±4.8	3.9±2.1	0.016[b]
RNFL	93.7±11.2	106.1±8.7	0.002[b,*]
CDR	0.5±0.2	0.2±0.1	0.000[b,*]
Metabolic parameters			
BMI	29.5±3.8	30.5±5.9	0.643[a]
Systole	129.2±11.5	140.8±20.9	0.129[a]
Diastole	79.2±8.2	78.7±7.9	0.800[c]
Waist circumference	95.8±8.2	93.7±8.9	0.549[a]
FBG	100.6±52.8	109.0±35.4	0.476[c]
HbA1c	6.0±1.6	5.7±1.6	0.421[c]
HDL	43.4±9.2	46.3±7.4	0.106[a]
LDL	143.6±54.2	150.8±34.2	0.363[a]
TG	170.8±124.2	160.5±63.5	0.854[b]
Cholesterol	193.5±50.2	205.4±37.2	0.476[a]
Biomarkers			
NLR	2.1±0.9	2.7±1.1	0.142[b]
TBARS	1.5±0.4	1.5±0.4	0.875[b]
FRAP	112.5±44.8	99.5±18.9	0.854[a]
Leptin	21956.5±14221.1	24461.3±21759.2	0.783[b]
Adiponectin	3.7±1.6	3.7±1.6	0.171[a]
hs-CRP	2.6±1.6	4.2±3.1	0.291[b]
ET-1	2.4±0.6	2.1±0.4	0.167[a]

Data were presented as mean±SD. [a]Data tested with two independent samples t-test; [b]Tested with Mann-Whitney U test. *Significant if *p*-value<0.05.

of multifactorial interaction, and numerous studies indicated that MetS could play a role in its pathogenesis. Metabolic syndrome increased oxidative stress and endothelial dysfunction, leading to the release of ET-1, inflammatory mediators, growth factors, and prothrombotic factors. These factors caused vasoconstriction, inflammation, vascular lesions, and remodeling, resulting in glaucomatous optic neuropathy (GON). The vasoconstriction was started by arteriovenous nicking, focal arteriolar narrowing, and enhanced arteriolar wall reflex, leading to a smaller diameter. The persistent vasospasms might cause microinfarctions which in turn led to visual field defects. When no microinfarction caused the axonal apoptosis effect, the visual field defect might not cause an increase in CDR, resulting in diffuse RNFL damage and thinning of lamina cribrosa.(14)

In glaucoma, the lamina cribrosa is where RGC axons and optic nerve fibers are most commonly damaged. The lamina cribosa creates the trans-lamina cribosa pressure differential (TLCPD), which is the pressure-shed of the intravitreal compartment with the IOP and the retro-lamina compartment with the optic nerve tissue pressure

Table 3. Significant correlation between the components of ocular parameters, metabolic parameters and biomarkers.

Parameters	r	*p*-value[a]
NTG		
MD – Systole	0.486	0.035*
CDR - Adiponectin	0.573	0.010*
CDR – ET-1	0.456	0.049*
Non-NTG		
MD - BMI	0.648	0.043*
CDR - LDL	-0.651	0.042*
CDR - TG	-0.679	0.031*

[a]Tested with Spearman correlation test. *Significant if *p*-value<0.05.

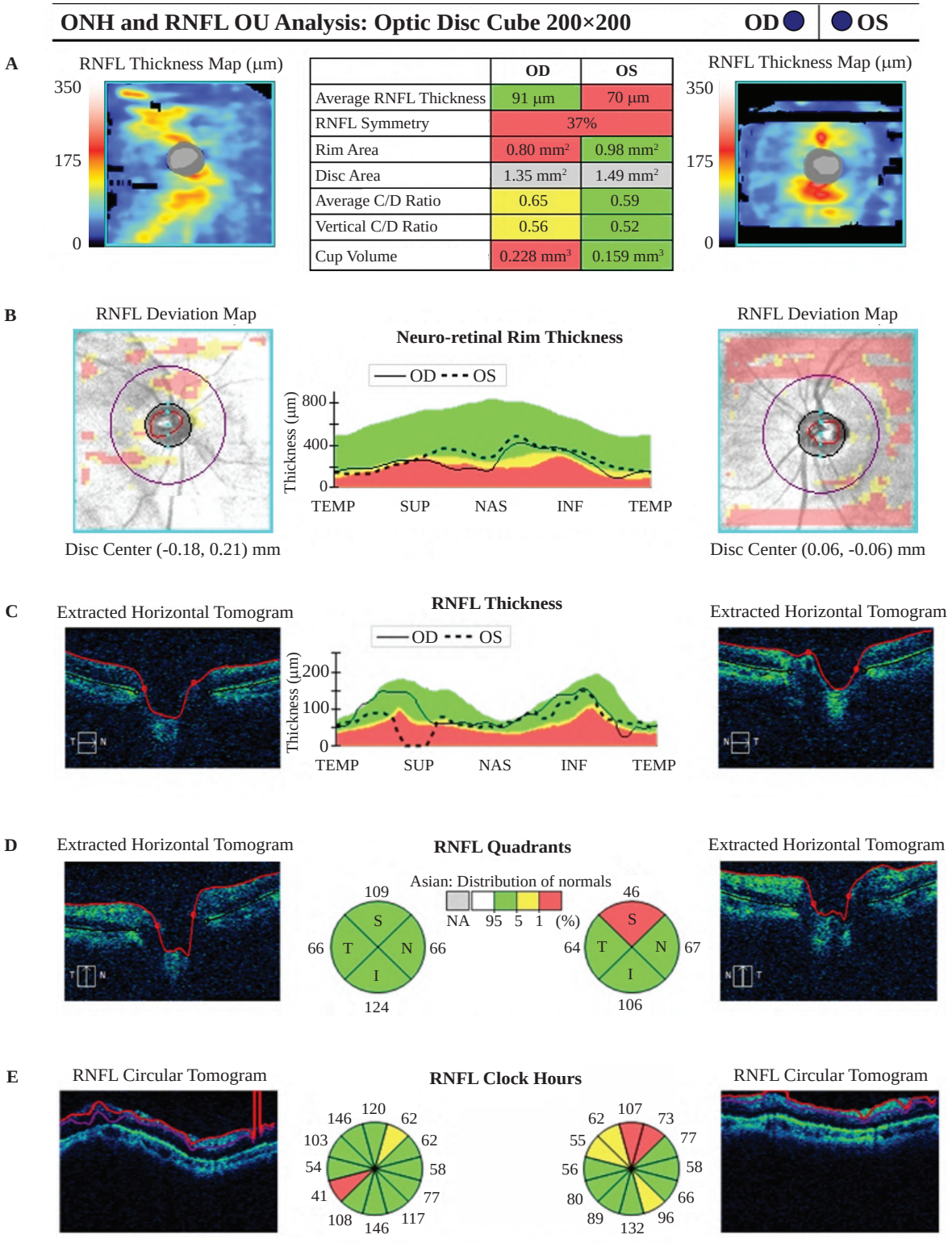

Figure 1. An example of an OCT result. A: RNFL thickness map; warm colors (red, and white) showed thicker RNFL, while cool colors (green, and blue) indicated thinner areas. B: RNFL deviation map; the Y-axis showed RNFL thickness in micrometers, while the X-axis represented different areas: temporal (TEMP), superior (SUP), nasal (NAS), and inferior (INF). In the RNFL thickness map, warm colors (red, and white) indicated thicker RNFL, and cool colors (green, and blue) indicated thinner RNFL. C: The extracted horizontal tomogram; the Y-axis showed RNFL thickness in micrometers, while the X-axis represented different areas: TEMP, SUP, NAS, and INF. The black circle indicated the Bruch membrane opening (BMO) placement, and the red line indicated the internal limiting membrane. A line from the black circle to the red circle was used to measure the minimal rim width (MRW). D: The extracted vertical tomogram; the red color in the neuro-retinal rim thickness quadrants section indicated thinning in the left eye's superior quadrant. E: RNFL circular tomogram, the RNFL clock hours map highlights statistical anomalies, marking areas thinner than normal in yellow or red.

and retrobulbar cerebrospinal fluid pressure (CSFP). This condition explained the barotraumatic mechanism in NTG, in which normal IOP and very low CSFP created an elevated TLCPD, leading to abnormal functioning of the optic nerve head due to changes in axonal transport and deformation of the lamina cribrosa.(4,15) The role of body weight and height, BMI, and arterial pressure in the development of glaucoma could be explained using the CSFP formula estimation, CSFP = 0.44×BMI (kg/m^2) + 0.16×diastolic pressure (mmHg) – 0.18×age (years) – 1.91. While TLCPD = IOP – CSFP. Thus, higher BMI and diastolic pressure might have a higher risk of developing glaucoma.(16)

One of the organs with the highest oxygen consumption is the retina, which depends more on aerobic glycolysis for metabolic processes. It has a high content of polyunsaturated fatty acids, and is responsive to a variety of stressors. This condition makes the retina vulnerable to free radical production-induced oxidative stress and lipid peroxidation. Oxidative stress will occur when the speed of free radicals' production, including reactive oxygen species (ROS) and reactive nitrogen species (RNS), exceeds the capacity of the cellular defense system. This condition causes damage to biological macromolecules, such as nucleic acids, lipids, and proteins, through peroxidation, crosslinking, breakage, and degeneration. Further, oxidative stress may induce endoplasmic reticulum stress, which works synergistically to drive glaucomatous damage to the trabecular meshwork, RGC, and the optic nerve head, leading to aggravated glaucoma.(4,6)

Adiponectin elicits an endothelium-dependent vasodilation of the retinal arterioles, and adiponectin receptor (AdipoR) is expressed in the endothelial cells of the retinal arterioles.(11) Further, our research showed that adiponectin was correlated with CDR, which may be due to the vasodilation of isolated retinal arterioles via the production of nitric oxide (NO), a powerful vasodilator of retinal arterioles, from the vascular endothelium. AdipoR1 and AdipoR2 are expressed in the vascular endothelial layer of the retinal arterioles. Therefore, we speculate that adiponectin can increase retinal blood flow by enhancing velocity through vasodilation of resistance vessels. However, unfortunately, then evidence on the role of adiponectin and leptin levels as key regulator in MetS and NTG has been lacking. Overall, these results imply that ET-1 may counteract adiponectin-regulated retinal circulation, indicating that further investigation is required into the association between ET-1 and adiponectin in the retinal circulation.

NTG started when vascular endothelial dysregulation induced ischemia of the optic nerve, which would activate microglia and astrocytes. Tumor necrosis factor (TNF)-α, NO, ET-1, glutamate, serine, and sodium were released into the extracellular space of the retina as a result of this situation, which had harmful consequences. ET-1 primarily acted as an autocrine/paracrine mediator, where its average plasma concentration was relatively low. Under pathological conditions, however, it could be produced enormously by a large number of cell types, including endothelial cells, vascular smooth muscle cells, and inflammatory cells such as macrophages and other leukocytes.(17,18) Studies reported that the systemic levels of ET-1 were significantly higher in the NTG group than in the control group. This elevation suggested a tendency for NTG patients to experience vascular endothelial dysfunction, oxidative stress, and imbalance in the metabolic homeostasis process, which was more severe than in patients without NTG.(19) This study found a significant positive correlation between ET-1 level with CDR (p=0.049); adiponectin and CDR in patients with NTG (p= 0.010). In another study, it was reported that ET-1 level was higher in NTG patients, which indicates its positive association with NTG. Consequently, ET-1 might be a good predictive biomarker or a target for pharmacological intervention.(20)

Furthermore, MD was correlated with systole blood pressure (p=0.035). This finding is consistent with prior research indicating that excessive blood pressure variability that exceeds the limit of normal vascular auto-regulation generates an ocular blood flow deficit, which leads to ischaemic optic nerve injury. As a result, various ways to regulating BP fluctuation and sufficient BP control appear to be crucial in glaucoma care. likewise, higher blood pressure fluctuation due to aberrant autonomic modulation of cardiovascular responses appears to be a risk factor for the early advancement of NTG.(21) Hypertensive individuals with NTG have trouble treating HTN with antihypertensives. Excessive BP control for cardiovascular risk may decrease ocular perfusion pressure and progress NTG. There are no clear management guidelines for NTG patients without HTN with higher systemic blood pressure fluctuations.(22)

In this study, majority of study subjects were NTG, previously unaware of the condition preventing them from seeking medical help. This condition indicated an iceberg phenomenon, in which many more people in the general population could have the same condition but did not visit healthcare facilities. Since 2014, Indonesia has provided

universal health coverage which is available in primary and advanced health care facilities. Currently, more than 10,000 primary health care centers in Indonesia are capable of conducting basic ophthalmology screening, including visual acuity and visual field tests. With the increasing proportion of the aging population in Indonesia.(1,23) This study suggested the importance of increasing community awareness to avert metabolic syndrome. Patients with metabolic syndrome had an increased risk of developing neuroinflammation and oxidative stress in the retina which led to POAG and ischemic optic neuropathy, and eventually irreversible damage to the optic nerve.(20,24,25) Therefore, they should participate in simple visual acuity and visual field examinations, such as a confrontation test at the primary healthcare level as an early detection program to prevent "the silent thief of sight" and blindness. This study had several limitations, including the use of a cross-sectional design in small sample size, and the inability to match overall samples for their onset of disease, severity, duration, and type of treatment received by the patients. Therefore, a multi-center study with a large sample size on the same topic using a matched case-control design or retrospective cohort is needed to address the constraints of this study.

Conclusion

There are correlation between adiponectin and ET-1 with NTG in MetS patients. Meanwhile, metabolic parameters including BMI, LDL and TG were correlated with control group. Therefore, adiponectin and ET-1 might be considered to be potential as early detection parameters for NTG in Mets patients.

Authors Contribution

SP contributed to conceptualization, methodology, investigation, manuscript preparation, and manuscript review. VDO contributed to the investigation and data validation. SN contributed to the investigation and data validation. WD contributed to methodology, statistical analysis, manuscript preparation, manuscript editing, and manuscript review. LR contributed to manuscript editing and review. BBS contributed to conceptualization and supervision. AS contributed to conceptualization, supervision, manuscript editing, and review. All authors approved the final version of the manuscript.

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