RELATIONSHIP BETWEEN METABOLIC COMPONENTS (FASTING BLOOD GLUCOSE LEVEL AND BLOOD PRESSURE) AND NORMAL-TENSION GLAUCOMA (NTG)

FINAL ASSIGNMENT

To Meet The Requirements and Obtain
The Title of Bachelor Of Medicine

By :
Kalaiyarasi A/P Vengadesan
155070108121008

MEDICINE STUDY PROGRAMME
FACULTY OF MEDICINE
BRAWIJAYA UNIVERSITY
MALANG

2019

TABLE OF CONTENTS

APPROVAL PAGE
FINAL ASSIGNMENT

RELATIONSHIP BETWEEN METABOLIC COMPONENTS (FASTING BLOOD GLUCOSE LEVEL AND BLOOD PRESSURE) AND NORMAL-TENSION GLAUCOMA (NTG)

To fulfill the Requirement for Degree of Bachelor of Medicine

By:
Kalaiyarasi A/P Vengadesan
155070108121008

Has been examined on:
Day: Wednesday
Tanggal : 18 December 2019
Approved by:

Examiner I

dr. Sony Agung Santoso, Sp.M (K)

NIP.196603111996011001

Advisor I/Examiner II

dr.Aulia Abdul Hamid,SpM

NIP.197706012003121005

Advisor II/ Examiner III

dr. Andhika Yudistira, Sp.OT (K)

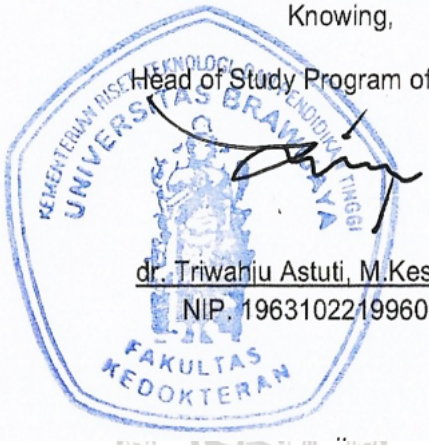
NIP.198305102009121002

Mengetahui,
Ketua Program Studi Pendidikan Dokter

dr. Triwahju Astuti, M.Kes., Sp.P(K)
NIP.196310221996012001

Knowing,

Head of Study Program of Medicine,



dr. Triwahju Astuti, M.Kes.,Sp.P(K).

NIP. 196310221996012001

ABSTRACT

Vengadesan, Kalaiyarasi. 2019. *Relationship Between Metabolic Components (Fasting Blood Glucose and Blood Pressure) and Normal-Tension Glaucoma (NTG)*. Final assignment, Medical Study Program, Faculty of Medicine, Universitas Brawijaya, Malang. Supervisors: (1) dr. Aulia Abdul Hamid, M.BiomedSc, Sp.M(K) (2) dr. Andhika Yudistira, Sp.OT(K).

Glaucoma refers to a group of eye diseases associated with characteristic structural damage to the optic nerve due to excessively high intraocular pressure (IOP). Metabolic syndrome (MS) is defined as a cluster of heart attack risk factors such as diabetes, pre-diabetes, obesity, high cholesterol and high blood pressure. The purpose of this study is to determine the relationship between metabolic components (fasting blood glucose and blood pressure) and normal-tension glaucoma. This study was an observational study with cross-sectional approach. The samples (30) were taken consequently from patients in Poli Mata RS Saiful Anwar who were diagnosed with metabolic syndrome. Their fasting glucose levels and blood pressure were measured. They are later sent to the Poli mata divisi Glaukoma dan Neurooftalmologi to test for normal-tension glaucoma. Shapiro-Wilk test is used because the data are less than 50. There results showed sig = 0.000 <0.05. Thus, the data is not normally distributed and Mann-Whitney test is used. The significance of SBP is 0.318, DBP is 0.316 and FBG is 0.191 which are more than 0.05 (sig.> 0.05). As the data was not normally distributed, it is normalized and T-test was used. The results showed the significance value of SBP, DBP and FBG are 0.955, 0.253 and 0.293 respectively which are >0.05. Based on the results, it is concluded that metabolic components, fasting blood glucose and blood pressure have no significant relationship with normal-tension glaucoma.

Keywords: Metabolic Syndrome, Normal-Tension Glaucoma, Fasting Blood Glucose, Blood Pressure

ABSTRAK

Vengadesan, Kalaiyarasi. 2019. *Relationship Between Metabolic Components (Fasting Blood Glucose and Blood Pressure) and Normal-Tension Glaucoma (NTG* Tugas Akhir, Program studi Kedokteran, Fakultas Kedokteran, Universitas Brawijaya, Malang. Pembimbing: (1) dr. Aulia Abdul Hamid, M.BiomedSc, Sp.M(K) (2) dr. Andhika Yudistira, Sp.OT(K).

Glaukoma merupkan sekelompok penyakit mata yang terkait dengan kerusakan struktural khas pada saraf optik karena tekanan intraokular yang terlalu tinggi (IOP). Sindroma metabolik (MS) didefinisikan sebagai sekelompok faktor risiko serangan jantung seperti diabetes, pra-diabetes, obesitas, kolesterol tinggi dan tekanan darah tinggi. Tujuan dari penelitian ini adalah untuk mengetahui hubungan antara komponen metabolisme (glukosa darah puasa dan tekanan darah) dan normo-tensi glaukoma. Penelitian ini adalah penelitian observasional dengan pendekatan cross-sectional. Sampel (30) diambil secara dari pasien di Poli Mata RS Saiful Anwar yang didiagnosis dengan sindroma metabolik. Kadar glukosa puasa dan tekanan darah mereka diukur. Mereka kemudian dikirim ke Poli mata divisi Glaukoma dan Neurooftalmologi untuk menguji normo-tensi glaukoma. Uji Shapiro-Wilk digunakan karena datanya kurang dari 50. Ada hasil yang menunjukkan sig = 0,000 <0,05. Dengan demikian, data tidak terdistribusi secara normal dan uji Mann-Whitney digunakan. Signifikansi SBP adalah 0,318, DBP 0,316 dan FBG adalah 0,191 yang lebih dari 0,05 (sig.> 0,05). Karena data tidak terdistribusi normal, dinormalisasi dan T-test digunakan. Hasil penelitian menunjukkan nilai signifikansi SBP, DBP dan FBG masing-masing adalah 0,955, 0,253 dan 0,293 yaitu> 0,05. Berdasarkan hasil, disimpulkan bahwa komponen metabolisme, glukosa darah puasa dan tekanan darah tidak memiliki hubungan yang signifikan dengan normo-tensi glaukoma.

Kata Kunci: Sindroma Metabolik, Normo-Tensi Glaukoma, Glukosa Darah Puasa, Tekanan Darah

CHAPTER 1

INTRODUCTION

1.1 Background

According to World Health Organization (WHO), glaucoma (12.3%) is the second leading cause of blindness in all areas of earth after cataract (47.9%) (WHO, 2004). Around 66.8 millions of the world's population are suffering from glaucoma.

Glaucoma refers to a group of eye diseases associated with characteristic structural damage to the optic nerve due to excessively high intraocular pressure (IOP). Although the exact theory of glaucoma is not clear, some factors such as high intraocular pressure (IOP), asymmetrical cup-disk ratio, and increased cup-disk ratio and disc hemorrhage are said to be behind glaucoma.

Metabolic syndrome (MS) is defined as a cluster of heart attack risk factors such as diabetes, pre-diabetes, obesity, high cholesterol and high blood pressure (International Diabetes Foundation, 2016). Current studies show that elevated intraocular pressure is associated with metabolic complications and insulin resistance (Oh SW, 2005). Although diabetes is associated with an elevated intraocular pressure (IOP), the underlying mechanisms are still unclear (The Glaucoma Foundation, 2015).

Only small amounts of people who are affected by glaucoma are aware about the disease because of its asymptomatic nature in the early stage. This results in delayed treatment and eventually causes blindness (Robert N, 2014).

The purpose of this study is to assess the relationship between metabolic components (fasting blood glucose level and blood pressure) and normal-tension glaucoma in patients with metabolic syndrome. The results of this study might contribute to an explanation about the relationship between glaucoma, intraocular pressure and metabolic syndrome. Therefore, it can be used in the treatment and prevention of glaucoma in metabolic syndrome patients.

1.2 Problem Formulation

What is the relationship between fasting blood glucose level and normal-tension glaucoma?

What is the relationship between blood pressure and normal-tension glaucoma?

1.3 Purpose of Research

1.3.1 General Purpose

To determine the relationship between metabolic components (fasting blood glucose level and blood pressure) and normal-tension.

1.3.2 Specific Purpose

a. To determine the relationship between fasting blood glucose level and normal-tension glaucoma (NTG).
b. To determine the relationship between blood pressure and normal-tension glaucoma (NTG).

1.4 Benefit of Research

1.4.1 Academic Benefits

a. To increase the knowledge about occurrence of glaucoma in elevated fasting blood glucose level and blood pressure.

b. Can serve as a theoretical basis to add knowledge for future research development in glaucoma.

1.4.2 Practical Benefits

a. Can be used as basis of early detection and prevention of glaucoma among metabolic patients.

CHAPTER 2

REVIEW OF LITERATURE

2.1 Metabolic Syndrome

2.1.1 Definition

Metabolic syndrome is a cluster of atherosclerotic risk factors that increase a person's chance of developing heart disease, diabetes and stroke. These factors include obesity, impaired glucose tolerance (IGT) or diabetes, hypertension, insulin resistance, dyslipidemia and hyperinsulinemia (K Imai et al., 2010).

2.1.2 Diagnostic Criteria

According to the National Cholesterol Education Program Third Adult Treatment Panel (NCEP ATP III), modified according to Asian populations, several criteria are included in the diagnostic criteria. Those criteria include waist circumference > 90cm for men and > 80cm for women, Triglyceride > 150mg/dL, HDL-C < 40mg/dL in men and < 50 mg/dL in women, systolic blood pressure > 130mmHg or diastolic blood pressure > 85mmHg or antihypertensive drug treatment and fasting blood glucose (FBG) > 100mg/dL (Grundy et al., 2005).

Table 2.1 Criteria for Clinical Diagnosis of Metabolic Syndrome (Grundy et al., 2005).

Measure	Categorical Cut Points
Elevated Waist Circumference[a]	≥ 102 cm in males≥ 88 cm in females
Elevated triglycerides(drug treatment for elevated triglycerides is an alternate indicator[b])	≥ 150 mg/dL (1.7 mmol/L)
Reduced HDL-C(drug treatment for reduced HDL-C is an alternate indicator[b])	< 40 mg/dL (1.0 mmol/L) in males< 50 mg/dL (1.3 mmol/L) in females
Elevated blood pressure(antihypertensive drug treatment in a patient with a history of hypertension is an alternate indicator	Systolic ≥ 130 and/or diastolic ≥ 85 mm Hg
Elevated fasting glucose[c](drug treatment of elevated glucose is an alternate indicator)	≥ 100 mg/dl

Table 2.2 Country/Ethnic Specific Values for Waist Circumference (Alberti G, 2006).

Country/Ethnic Group	Waist Circumference (as Measure of Central Obesity)
Europeans	Male ≥94 cm Female ≥80 cm
South Asians	Male ≥90 cm Female ≥80 cm
Chinese	Male ≥90 cm Female ≥80 cm
Japanese	Male ≥85 cm Female ≥90 cm

*These are pragmatic cut points and better data are required to link them to risk. Ethnicity should be the basis for classification, not the country of residence.

2.2 Glaucoma

2.2.1 Definition

Glaucoma is a group of disorders characterized by a progressive optic neuropathy resulting in characteristic changes in the optic nerve head and corresponding loss of visual field that are associated frequently but not invariably with raised intraocular pressure (IOP). IOP is the most common risk factor. However, it is not the only risk factor for development of glaucoma. In cases with raised IOP without any associated glaucomatous damage, the term 'ocular hypertension' is used (A K Khurana, 2007).

2.2.2 Classification

A. Primary Open Angle Glaucoma (POAG)

POAG is a type of primary glaucoma. There is no obvious systemic or ocular cause of rise in the intraocular pressure (IOP). POAG occurs in eyes with open angle of the anterior chamber. POAG is also a chronic simple glaucoma of adult onset. It is characterized by slowly progressive raised intraocular pressure (>21 mmHg recorded on at least a few occasions) associated with characteristic optic disc cupping and specific visual field defects (A K Khurana, 2007). POAG usually has no symptoms. The rise of pressure in the eye is slow and the cornea adapts without swelling. Thus, this disease often goes undetected. In addition, it is painless and the patient often does not realize about the condition until the disease reaches the later stages. Hence, the damage is irreversible by the time the vision is impaired (The Glaucoma Foundation, 2018). In order to prevent this, it is advisable that all patients over 40 years old to get periodic measurement of intraocular pressure (IOP). Furthermore, relatives of patients with chronic open-angle glaucoma should be reviewed regularly. As for the treatment for glaucoma, it can be either medical, via laser or surgical. Medical treatment of glaucoma aims to control the intraocular pressure (IOP) with the use of eye drops. The eye drops acts by inhibiting the production of aqueous or promoting greater aqueous outflow. When medical treatment fails or unsatisfactory, laser trabeculoplasty may be used. It involves laser treatment of trabecular meshwork. In case both the medical treatment and laser trabeculoplasty are ineffective, trabeculectomy is performed (Arthur, 2007).

B. Normal Tension Glaucoma (NTG)

Normal tension glaucoma (NTG) is a variant of POAG. It is also known as low tension glaucoma. It happens when typical glaucomatous disc changes with or without visual field defects and associated with an intraocular pressure (IOP) constantly below 21 mmHg. Characteristically the angle of anterior chamber is open on gonioscopy and there is no secondary cause for glaucomatous disc changes. NTG is a result of chronic low vascular perfusion, which subsequently makes the optic nerve head susceptible to normal intraocular pressure (IOP). Medical treatment aims to lower IOP by 30% (12-14 mmHg). Betaxolol is the drug of choice because other than lowering IOP, it also increases optic nerve blood flow. Apart from that, when progressive field loss occurs despite IOP in lower teens, trabeculectomy may be considered. In patients with confirmed peripheral vasospasm, systemic calcium channel blockers such as nifedipine can be used (A K Khurana, 2007).

C. Primary Angle-Closure Glaucoma (PACG)

Primary angle-closure glaucoma (PACG) is characterized by elevated IOP resulting from partial or complete occlusion of the angle by the iris (James C. Tsai, 2011). The rise in intraocular pressure occurs when the aqueous humor outflow is blocked by closure of a narrower angle of the anterior chamber. According to clinical presentation, the PACG can be classified into five different clinical groups: latent primary angle-closure glaucoma, subacute (intermittent) primary angle-closure glaucoma, acute primary angle-closure glaucoma, postcongestive angle-closure glaucoma, chronic primary angle-closure glaucoma and absolute glaucoma (A K Khurana, 2007).

D. Secondary Glaucoma

In secondary glaucoma, a disease that blocks the outflow channel of the aqueous may increase the intraocular pressure (IOP). For example, in severe iridocyclitis, the inflammatory proteins and cells or iris adhesions may block up the outflow channel. In hyphema where there is blood in the anterior chamber, the blood may block the outflow channel. Rubeosis iridis, which may develop following central retinal vein occlusion and proliferative diabetic retinopathy, may lead to secondary hemorrhagic glaucoma (neovascular glaucoma). At times, glaucoma is a complication of a mature cataract or intraocular tumors (Arthur, 2007).

2.2.3 Epidemiology

It is estimated that by the year 2020, there will be almost 80 million people in the world with open-angle glaucoma and angle-closure glaucoma. The majority of them will have open-angle glaucoma. It is predicted that 70% of the angle-closure glaucoma will be women and 87% will be Asian. Bilateral blindness from glaucoma is estimated to affect greater than 11 million individuals worldwide by 2020. It is believed globally that glaucoma is a significant cause of vision loss that disproportionately affects Asians and women. Risk factors for open-angle glaucoma include increased age, family history, African ethnicity, increased intraocular pressure, decreased corneal thickness and myopia. However, risk factors for angle closure glaucoma include Inuit and Asian ethnicity, female sex, hyperopia, small corneal diameter, shallow anterior chamber, short axial length, steep corneal curvature, shallow limbal chamber depth, and thick, relatively anteriorly positioned lens (Singh, 2004).

2.2.4 Diagnosis

A. Structural Changes

Cross-section demonstrates the optic nerve head (optic disc) has a central depression where the retinal vessels enter the eye. It is known as the 'cup'. When peripheral nerve fibres are lost in glaucoma, the remaining fibres take their places and leave a larger 'cup'. There is a progressive 'cupping' of the optic nerve head when progressive axonal loss. This is the end result of fully cupped disc is the disc with cavernous optic atrophy. Cupping of the optic disc may be seen on fundoscopy. It shows as an area of central pallor. The ratio of the cup size to the disc size demonstrated the degree of cupping. The degree of some cupping is normal and some have physiologically enlarged cups. Therefore, cupping is suspicious if the cup/disc ratio is more than 0.5, the vertical cup/disc ratio is more than the horizontal cup/disc ratio and there is asymmetry between the cup/disc ratios of the two eyes of more than 0.2 (Williams S, 2007).

Colour photography, stereoscopic photography, optical coherence tomography (OCT), and confocal scanning laser ophthalmoscopy (Heidelberg Retina Tomograph or HRT) can be used for objective assessments. These last two can also be used to evaluate the thickness of the retinal nerve fibre layer (RNFL) that surrounds the optic disc. The thinning of the peripapillary retinal nerve fibre layer (RNFL) is a sensitive indicator of glaucomatous axonal loss. Scanning laser polarimetry (Nerve Fiber Analyser or GDx VCC) can be used to assess this. However, the diagnosis of glaucoma cannot be made on solely based on structural changes alone. Thus, diagnosis tests demonstrating functional changes are also required alongside structural changes to diagnose glaucoma (Williams S, 2007).

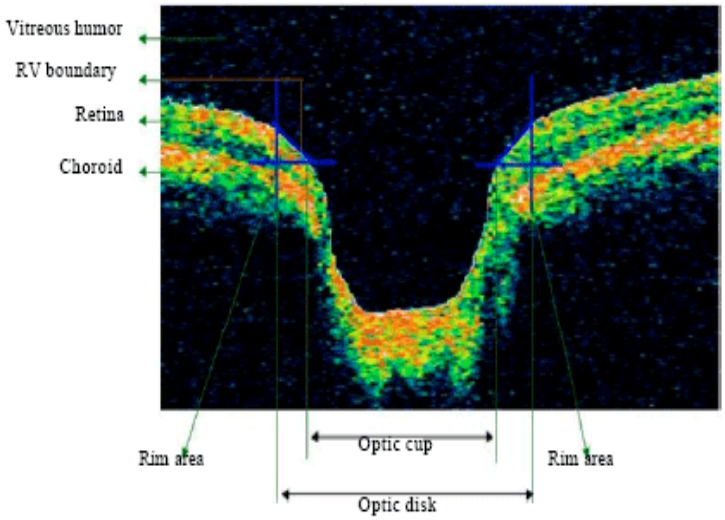


Figure 2.1 OCT of the optic nerve head showing the cup (Ganesh B, 2012).

B. Functional Changes

The axonal loss begins with axons in the periphery of the nerve. These axons originate in the retinal ganglion cells in the retinal mid-periphery with consequent visual field fallout in these regions. The scotomas that develop in the visual field often go unnoticed by patients. Formal automated perimetry (visual field testing) is used to detect these scotomas. In formal automated perimetry, the patient is presented with targets of differing intensity at different points within their visual field. A best way to assess the visual field is to look at the grey-scale representation of the field. The normal visual field is called a 'hill' of vision with the best acuity at fixation tailing out to the periphery. The 'blind spot' refers to the optic nerve head. It is located at about 15 degrees temporal to the fixation point (Williams S, 2007).

There is initially an enlargement of the blind spot followed by mid-peripheral 'arcuate' scotomas in glaucoma. In end-stage glaucoma, the patients have tunnel vision when all but the central area of fixation is involved. At this stage, the patient may still have a normal visual acuity when tested on a Snellen chart although there

is enormous fallout of visual field. However, this type of testing has limitations because it is subjective, requires concentrations and does not detect early damage. Thus, tests such as short wavelength automated perimetry (SWAP), frequency doubling technology (FDT) and multifocal visual evoked potentials (mVEP) should be used.

C. Intraocular Pressure (IOP)

Tonometry is used to measure the pressure within the eye. Firstly, eye drops are used to numb the eye (anesthetic). Then, a device called a tonometer is used to measure the inner pressure of the eye. A small amount of pressure is applied to the eye by a tiny device. The range for normal pressure is 12-22 mmHg. Most of the glaucoma cases show pressure that exceeds 20mmHg. However, there are some people can have glaucoma at pressures between 12-22mmHg (Glaucoma Research Foundation, 2017). Intraocular pressure (IOP) is determined by aqueous humour production and outflow. Ciliary body produces aqueous humour. Aqueous humor flows over the lens into the anterior chamber of the eye. The trabecular meshwork lies circumferentially in the angle of the eye. 90% of aqueous humor exits the eye through trabecular meshwork into the canal of Schlemm. The canal of Schlemm connects to the episcleral venous circulation through aqueous veins. The remaining aqueous exits the eye directly via uveoscleral outflow. Aqueous production is usually constant. Therefore, a raised IOP is the result of increased resistance to outflow at the trabecular meshwork level (Williams S, 2007).

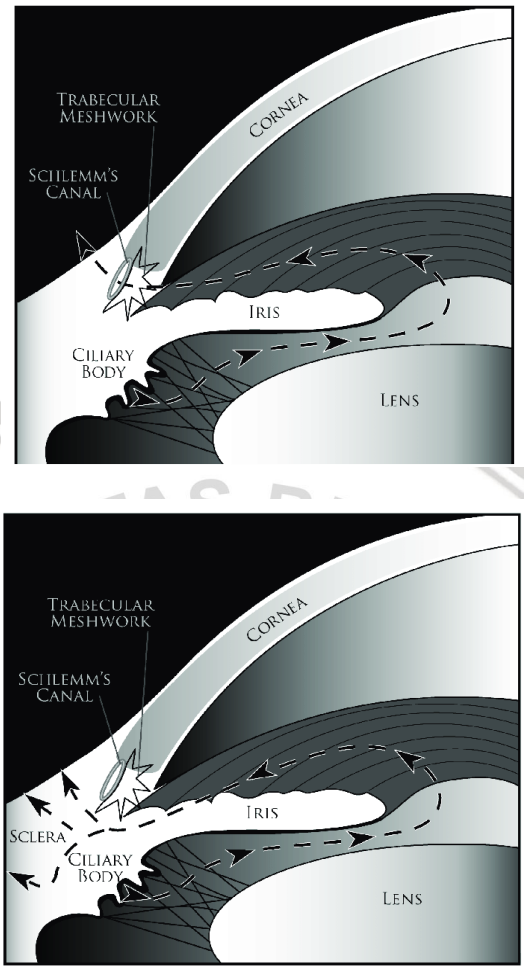


Figure 2.2 The drainage angle - aqueous humor dynamics (Goel M, 2010).

2.3 Relationship between Fasting Glucose, Metabolic Syndrome and Glaucoma

Studies were conducted in order to determine if elevated fasting blood glucose level that is a parameter of metabolic syndrome has positive associations with increased intraocular pressure (IOP) and glaucoma. However, the mechanisms relating fasting blood glucose level to increased IOP are unclear. Increased intraocular pressure (IOP) in metabolic syndrome may be the result of hyperglycemia, which in turn may induce an osmotic gradient that draws excess

aqueous humor into the anterior chamber and to autonomic dysfunction. Moreover, hyperglycemia also may increase IOP by interrupting the trabecular meshwork function. Nonetheless, the association between diabetes and IOP was weak, suggesting that the association between diabetes and glaucoma in part may be independent of raised IOP (Di Zhao et al., 2015). Thus, further researches are needed to study the relationship between fasting blood glucose, metabolic syndrome and glaucoma.

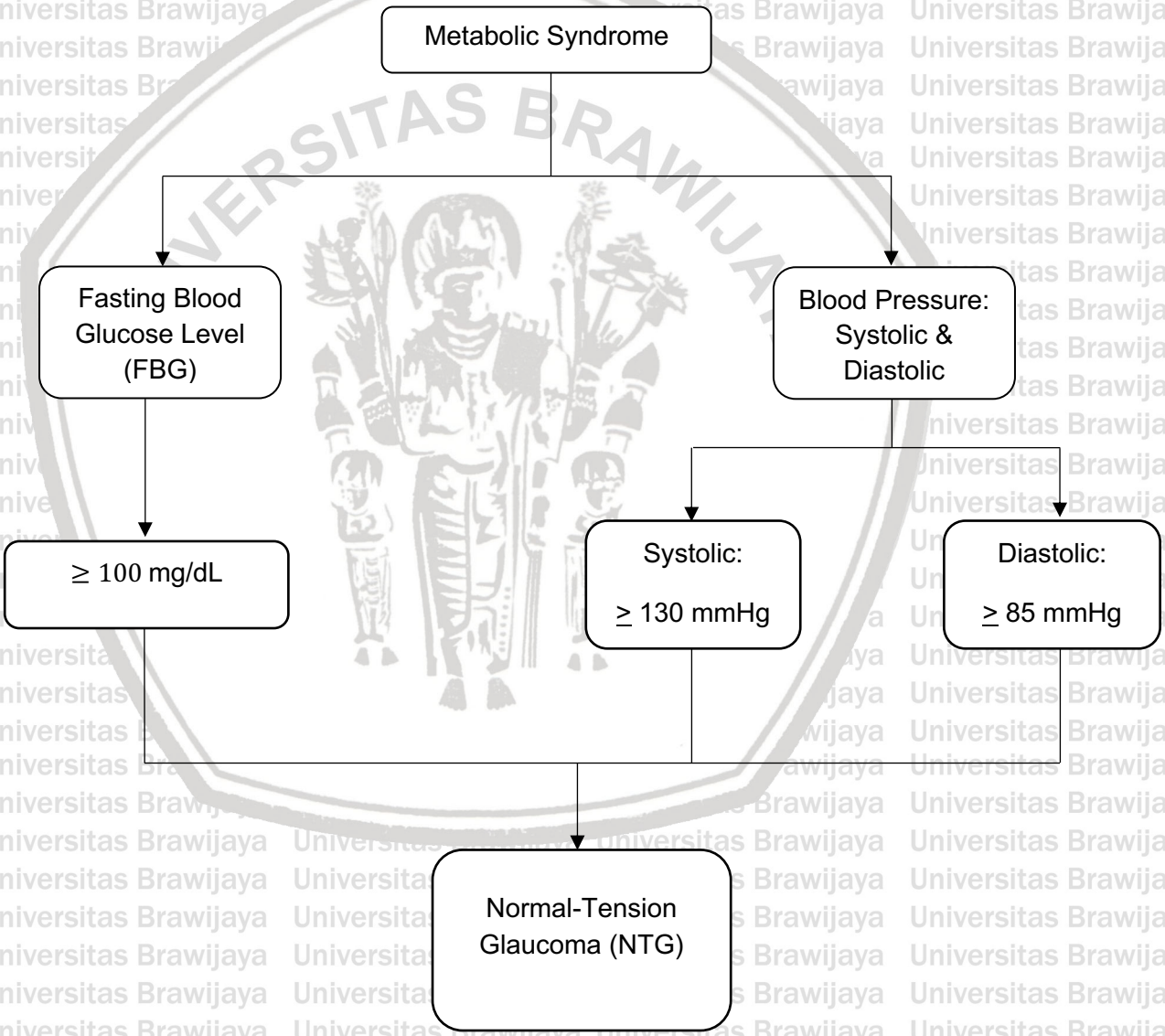
2.4 Relationship between Blood Pressure and Glaucoma

Studies have suggested possible mechanisms for the association between cardiovascular risk factors and elevated IOP. In particular, hypertension is linked to an elevated IOP in a physiological manner; SBP, rather than DBP, elevates IOP because peaks of SBP that reach the eye can lead to ultrafiltration. However, other studies have implied that ocular perfusion pressure seems more pertinent to glaucoma than BP alone, and relationship of BP and OAG may be affected by many complex factors. Therefore, further studies are needed to confirm the relationship between blood pressure and glaucoma.

CHAPTER 3

CONCEPTUAL FRAMEWORK AND HYPOTHESIS

3.1 Conceptual Framework



3.2 Hypothesis

Increased level of fasting glucose and high blood pressure increases the risk of developing normal-tension glaucoma.

CHAPTER 4

RESEARCH METHOD

4.1 Research Design

The study design used is observational study with cross-sectional approach. The purpose was to determine the relationship between metabolic components (fasting blood glucose level and blood pressure) and normal-tension glaucoma.

4.2 Locations and Period of Research

This research was be conducted at Outpatient Clinic for Internal Medicine and Outpatient Clinic of Ophthalmology in Saiful Anwar Hospital from December 2017 to March 2018.

4.2.1 Sample Size Estimation

The number of samples was determined by Lemeshow Formula:

$$n = \frac{Z_\alpha^2 \, p \, q}{d^2} = \frac{Z^2 p(1-p)}{d^2}$$

Information:

n = minimum number of samples needed

Z = degree of trust (1.64 for α = 0.1)

P = proportion of people with optic neuropathy (6%)

q = proportion of people who are not sufferers of optic neuropathy

d = limit of error or absolute precision (α = 0.1)

From the calculation results, the minimum sample size is 15.17 or rounded up to 15 patients.

4.3 Sample Selection

The sample of this research was taken consequently from patients in Outpatient Clinic of Endocrinology and Ophthalmology in Saiful Anwar Hospital. Their fasting glucose levels and blood pressure were measured. They were later sent to the Glaucoma and Neuro-ophthalmology Department to test for normal-tension glaucoma (NTG). They were later subdivided into two groups:

I. With normal-tension glaucoma

II. Without normal-tension glaucoma

4.4 Inclusion and Exclusion Criteria

Inclusion Criteria

- Age > 40 years old.
- Fulfill the diagnostic criteria of Metabolic Syndrome based on IDF:

  Central obesity (abdominal circumference> 90 cm for Asian men and abdominal circumference> 80 cm for Asian women) plus 2 of the following 4 factors:

  (1) Triglycerides> 150 mg / dL (1.7 mmol / L) or being treated for hypertriglyceridemia;

(2) HDL-C: <40 mg / dL (1.03 mmol / L) in men and <50 mg / dL (1.29 mmol / L) in women or under treatment for elevated HDL-C levels;

(3) Blood pressure: systolic> 130 mmHg or diastolic> 85 mmHg or moderate in the treatment of hypertension;

(4) Fasting blood sugar (FBG)> 100 mg / dL (5.6 mmol / L), or type 2.14 diabetes.

- Patients are willing to be taken blood for measuring fasting blood glucose.
- Willing to give approval as a research sample.
- There are no systemic complications from metabolic syndrome.

Exclusion Criteria

- Presence of other optic neuropathy other than glaucoma.
- The results of diagnostic investigations are incomplete.
- The patient refused to take part in the research as a sample.

4.5 Variables

4.5.1 Independent Variable

The independent variable of this research is fasting glucose level and blood pressure.

4.5.2 Dependent Variable

The dependent variable of this research is occurrence of normal-tension glaucoma among the metabolic syndrome patients.

4.5.3 Operational Definition

- Diagnosis of glaucoma is the diagnosis of the patient established by history taking, physical examination, ophthalmological examination (anterior segment and fundoscopy), intraocular pressure examination (IOP), perimetry and OCT, and diagnosed by one of the supervisors of Glaucoma Subdivision Poli Mata RSSA.
- Metabolic syndrome: is a collection of risk factors based on the components and criteria of the IDF (International Diabetes Federation) in 2006, namely: Central obesity (as measured by abdominal circumference whose normal values are based on specific ethnicity), added by at least 2 of the following 4 factors :
  I. Increase in triglycerides: ≥ 150 mg / dL (or therapy for dyslipidemia)
  II. Decrease in cholesterol HDL: <40 mg / dL (male) or <50 mg / dL (female) (or get therapy for dyslipidemia).
  III. Increase in blood pressure: systole ≥ 130 or diastole ≥85 mmHg (or therapy for hypertension).
  IV. Increased fasting blood sugar: ≥ 100 mg / dL.
- In this study, the component of the metabolic syndrome used was an increase in fasting blood sugar levels.

4.6 Instruments and Materials

I. Snellen chart
II. Application tonometer (Haag streit AT 900 scale value 1.96 mN CE 0124)
III. Direct fundoscopy (Neitz Halogen Ophthalmoscope BX α)

IV. Gonioscopy Thorpe 4

V. Slitlamp

VI. OCT (OCT Cirrus HD-5000)

VII. Humphrey Perimetry (Carl Zeiss Meditec HFA II 750-31257-5.1,1)

VIII. Disposable syringes

IX. Blood vacutainer tubes

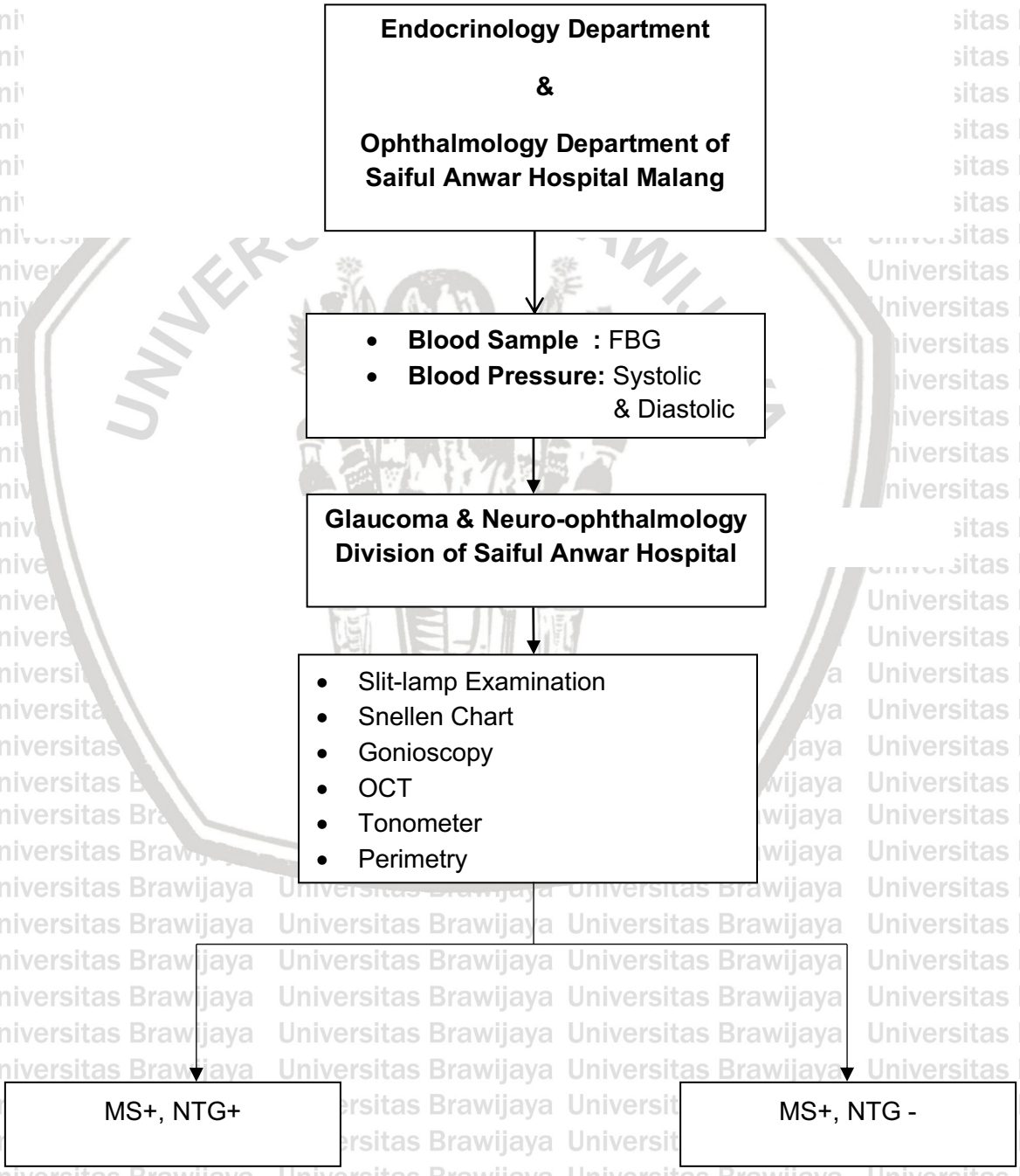
4.7 Research Procedures

The research was conducted by collecting blood samples and measuring the fasting blood glucose and blood pressure. The blood sample were taken after an overnight fast. A fasting blood sugar level less than 100 mg/dL (5.6 mmol/L) is normal. A fasting blood sugar level from 100 to 125 mg/dL (5.6 to 6.9 mmol/L) is considered prediabetes. If it's 126 mg/dL (7 mmol/L) or higher on two separate tests, you have diabetes. Then, the patients were checked if they have glaucoma by measuring IOP with the help with tonometer, fundoscopy and OCT. The blood pressure of the patients were measured. Patients with systolic blood pressure ≥ 130mmHg or diastolic blood pressure ≥85 mmHg were checked if they have NTG.

4.8 Data Collection and Statistical Analysis

Samples were collected by purposive random sampling. Normality test used is the Kolmogorov Smirnov test. Bivariate analysis was used to see the relationship between Systolic BP and FBG with NTG by using a statistical test, Spearman Correlation Test with the SPSS 21.00 program for windows.

4.9 Research Flow



CHAPTER 5

RESEARCH RESULTS AND DATA ANALYSIS

This chapter discusses the results of research and data analysis on the relationship between blood pressure and fasting blood glucose level with NTG. This research was conducted at Saiful Anwar Hospital Malang to calculate blood pressure and fasting blood glucose with NTG. The research was conducted between December 2017- March 2018.

5.1 Univariate Analysis

The following is an explanation of the results of the univariate analysis which includes respondents' demographic data.

5.1.1 Demographic data

Patient demographic data were obtained by age, sex.

Table 5.1 Frequency distribution of Patient demographic data at Saiful Anwar Hospital.

Gender	MS	%	MS+NTG	%
Female	9	60.00	8	53.33
Male	6	40.00	7	46.67

Based on table 5.1, it can be seen that patients with female sex with MS were 9 patients (60%) and those with MS + NTG were 8 patients (53.33%). Whereas

patients with male sex with MS were 6 patients 40%, and those with MS + NTG were 7 patients (46.67%).

Table 5.2 Patient Descriptive Statistics at Saiful Anwar Hospital

Parameter	Group	Mean ± sd	95% CI for Mean	
			Lower Bound	Upper Bound
Age	MS	49.60 ± 6.82	45.82	53.38
	MS+NTG	61.07 ± 9.26	55.94	66.20
Systolic BP	MS	132.33 ± 14.25	124.44	140.23
	MS+NTG	130.00 ± 13.50	122.53	137.47
Diastolic BP	MS	85.33 ± 11.87	78.76	91.91
	MS+NTG	81.00 ± 7.61	76.79	85.21
FBG	MS	113.47 ± 30.49	96.58	130.35
	MS+NTG	99.07 ± 15.07	90.72	107.41

5.2 Normality Test

This test is conducted to determine whether the residual value is spread normally or not. The test procedure is carried out by the Kolmogorov-Smirnov test, with the following conditions:

The hypothesis used:

H0: Data is spread normally

H1: Data is not spread normally

If the value of sig. (p-value)> 0.05, then H0 is accepted, which means that normality is fulfilled.

The results of the normality test can be seen in Table 5.3

Table 5.3: Normality Test Results

	Shapiro-Wilk		
	Statistic	df	Sig.
Systolic BP	.946	30	.134
Diastolic BP	.800	30	.000
FBG	.783	30	.000

Source: Primary data processed

From the results above, sig. Systolic BP is 0.134 (can be seen in Table 5.4) or greater than 0.05; then the provisions of H0 are accepted, that the assumption of normality is fulfilled. But for Diastolic BP and FBG sig. smaller than 0.05. So, for Diastolic BP and FBG, statistical measurements using parametric statistics with the Mann Mann Whitney test is used.

5.2.1 Testing the Difference between MS and MS + NTG

To know the difference between MS and NTG, the statistical tool for the average difference test, which is the unpaired t-test is used, because it is assumed that MS and NTG are mutually independent (not affecting each other).

Calculation of the unpaired t-test using the help of SPSS software version 20.00, so the results obtained in Table 5.4 below:

Table 5.4
Independent T-test

Parameter	NTG	N	Mean	Std. Deviation	t	p
Systolic BP	MS	15	132.333	14.251	0.460	0.649
	MS+NTG	15	130.000	13.496		
Diastolic BP	MS	15	85.333	11.872	0.460	0.316
	MS+NTG	15	81.000	7.606		
FBG	MS	15	113.467	30.486	0.460	0.191
	MS+NTG	15	99.067	15.069		

Based on the Table 5.4, t-test results obtained t-test results for Systolic BP of 0.460 and p value of 0.649 and because the value of p (0.649)> α = 5%, then H0 is accepted. So, it can be concluded that there are insignificant differences between MS and MS + NTG.

Mann Whitney test calculations using the help of SPSS software version 20.00 obtained results as shown in the following Table 5.5:

Table 5.5
Mann Whitney Test

Parameter	NTG	N	Mean	Std. Deviation	t	p
Diastolic BP	MS	15	85.333	11.872	0.460	0.316
	MS+NTG	15	81.000	7.606		
FBG	MS	15	113.467	30.486	0.460	0.191
	MS+NTG	15	99.067	15.069		

Based on the Table 5.5, Mann Whitney test results obtained for Diastolic BP is with a p value of 0.316 and because the value of p (0.316)> α = 5%, then H0 is accepted. So, it can be concluded that there are insignificant differences between MS and MS + NTG.

Based on the Table 5.5, the Mann Whitney test results for FBG is with a p value of 0.191 and because the value of p (0.191)> α = 5%, then H0 is accepted. So, it can be concluded that there are insignificant differences between MS and MS + NTG.

5.3 Correlation Analysis

Bivariate analysis was used to see the relationship between Systolic BP and FBG with NTG by using a statistical test, Spearman Correlation Test with the SPSS 21.00 program for windows.

Spearman's correlation is used in analyzing the relationship between the two variables. In this study there are two sources of data, namely variable X and variable Y.

In the correlation test, there are two hypotheses that can be used:

1. H0: there is an insignificant relationship (correlation) between Variable X and Variable Y

2. H1: There is a significant correlation (correlation) between Variable X and Variable Y

Table 5.6

Correlation Guideline

Coefficient interval	Relationship Level
0,00 – 0,199	Very Low
0,20 – 0,399	Low
0,40 – 0,599	Moderate
0,60 – 0,799	Strong
0,80 – 1,000	Very Strong

The results of the correlation test between the variables, Systolic BP and FBG with NTG using the Spearman correlation are shown in Table 5.7.

Table 5.7

Correlation of Systolic BP and FBG with NTG

Variable Relationship	r Spearman	p-value
Systolic BP - NTG	-0,186	0.326
FBG - NTG	-0.243	0.196

a. Correlation between Systolic BP and NTG

From the results in Table 5.7, it can be seen that the value of the Spearman correlation coefficient is negative, that is -0.186. Negative direction means that when the Systolic BP variable increases, the patient who tends to have NTG decreases. The resulting correlation coefficient shows the magnitude of the relationship of 0.186. This correlation value indicates that the relationship between Systolic BP and NTG variables is in the very low category. Based on the test results above, it can be seen that the p-value is greater than alpha 5% (0.326> 0.05), so H0 is accepted with the conclusion that there is a correlation between Systolic BP and NTG which is not significant.

b. Correlation between FBG and NTG

From the results in Table 5.7, it can be seen that the Spearman correlation coefficient is negative, that is -0.243. Negative direction means when the FBG variable increases, then the patient who tends to have NTG decreases. The resulting correlation coefficient shows the magnitude of the relationship of 0.243. This correlation value indicates that the relationship between the FBG variable and NTG is in the low category. Based on the above test results, it can be seen that

the p-value is greater than alpha 5% (0.196> 0.05), so that H0 is accepted with the conclusion that there is a correlation between FBG with NTG which is not significant.

CHAPTER 6
DISCUSSION

The aim of this research is to investigate the relationship between metabolic components (blood pressure and fasting blood glucose) and normal-tension glaucoma. The sample of this research was taken consequently from patients in Ophthalmology Department and Endocrinology Departments of Saiful Anwar Hospital Malang who were diagnosed with metabolic syndrome. Their fasting glucose levels and blood pressure were measured. They were later sent to the Glaucoma and Neuro-ophthalmology Division to test for normal-tension glaucoma.

6.1 Fasting Blood Glucose (FBG) and Normal-Tension Glaucoma (NTG)

This study has demonstrated that fasting blood glucose level (FBG), which is one of the components of metabolic syndrome, has no significant effect on the occurrence of normal-tension glaucoma (NTG). Subjects with metabolic component, in this case fasting blood glucose level (FBG) > 100mg/dL, has the same probability of getting NTG as those with normal FBG.

The results of current study correspond well with some earlier studies, where the history of diabetes mellitus (DM) appeared to be significantly protective against developing glaucoma (Gordon et al., 2002). In another population-based study, the association between diabetes mellitus and glaucoma was also unclear (Tielsch et

al., 1995). One of the previous longitudinal study also do not confirm diabetes mellitus or fasting blood glucose as a risk factor for the incidence of glaucoma.

However, some other studies have found significant association between fasting blood glucose and normal-tension glaucoma. In a previous study which investigated the association between impaired glucose tolerance (IGT) and normal-tension glaucoma (NTG), demonstrated that high IGT was associated with an increased prevalence of NTG. Those subjects in that study with higher IGT had an higher odds ratio for developing NTG. Also, some other earlier studies demonstrated that diabetes mellitus increases the risk of developing open angle glaucoma (Newman-Casey et al., 2011; Bonovas et al., 2004; Nakamura et al., 2005; Chopra et al., 2008; Klein et al., 1994; Pasquale & Kang, 2009).

It is also reasonable to suggest that diabetes has an association with glaucoma because impaired autoregulation is assumed to play an important role in the development of glaucoma (Suh et al., 2009; Flammer et al., 2002; Grieshaber & Flammer, 2005). Another study by Barbara (1994) concluded that the presence of open angle glaucoma is increased in older-onset diabetes. Moreover, in a study that investigated the prevalence of glaucoma and type 1 and type 2 diabetes, it was concluded that neurovascular glaucoma has a positive correlation with diabetic microvascular complications (Nielsen N.V. et al., 1983). In addition to that, high levels of blood glucose and newly diagnosed diabetes mellitus are proven to have an association with elevated intraocular pressure (IOP) and high-tension glaucoma (Dielemans I. et al., 1996).

In another analysis, components of metabolic syndrome especially elevated FBG caused higher IOP levels than subjects with normal FBG and consequently

cause glaucoma. Although the exact mechanism underlying this association is unclear, it is assumed that hyperglycemia increases production of fibronectin in the trabecular meshwork which may increase the resistance to aqueous humour flow and hence leads to an elevated IOP. Moreover, hyperglycemia is believed to cause apoptosis in retinal neuronal cells via the hexosamine biosynthetic pathway. The study also suggested that oxidative stress induced by hyperglycemia and end products of advanced glycation may increase death of retinal neurons by apoptosis (Rasoulinejad S.A. et al., 2015).

It has also been demonstrated in studies that diabetes mellitus is associated with primary open angle glaucoma (POAG). There is evidence that shows that the presence of long-standing elevated FBG alongside dyslipidemia increases the risk of neuronal injury from stress (Kong G.Y. et al., 2009; Fan N. et al., 2015). Next, some studies suggested that the capacity to auto-regulate blood flow may decrease in diabetic eyes and will reduce retinal blood flow. As a result, in order to elevated intraocular pressure (IOP), relative hypoxia occurs in diabetic eyes and causes the levels of hypoxia- inducible factor-1 (HIF-1α) to increase in retinal ganglion cells, and in the optic nerve head of glaucomatous eyes (Arjamaa O. et al., 2006). Other than that, there is another theory, suggests that diabetes mellitus may exacerbate remodelling of connective tissue. This reduces compliance at trabecular meshwork and subsequently increases the IOP and decreases compliance of lamina cribrosa which in turn causes higher mechanical stress on the optic nerve head (Roberts M.D. et al., 2009).

Although some previous studies support the findings of the current study, there are many other studies that show contradicting results. Therefore, further studies

are needed to be conducted to investigate the relationship between fasting blood glucose and normal-tension glaucoma (NTG) for better understanding.

6.2 Blood Pressure and Normal-Tension Glaucoma

This study has demonstrated that blood pressure which is one of the components of metabolic syndrome, has no significant effect on the occurrence of normal-tension glaucoma (NTG). Blood pressure (systolic and diastolic) has no effect on both subjects with or without normal-tension glaucoma (NTG).

Some studies demonstrated the same results as the current study. For example, in the Barbados Eye Study, it has been suggested than hypertension plays a protective role from developing glaucoma. Hypertension maintains an adequate perfusion for the optic nerve in that study (Leske et al., 2002). There are also studies that suggests that diastolic blood pressure has a positive relation to glaucoma whereas systolic blood pressure is said to have a negative relation to glaucoma (Katz & Sommer, 1988).

On the contrary, in a study that investigated whether or not metabolic syndrome is a risk factor for NTG, it was obtained that the prevalence of NTG was greater in subjects with hypertension than subjects without hypertension. The correlation was even greater when condition of the subjects comorbid with diabetes mellitus (Kim M. et al., 2014). A previous longitudinal study suggested the same, in which hypertension increases the chance of developing NTG by 17% and even more (48%) when comorbid conditions like diabetes mellitus and hyperlipidemia exist.

There are several theories that explained this. One of the theories suggests that

when the blood pressure increases, the ciliary artery perfusion also increases. This situation increases the risk of glaucoma. Patients with hypertension also are believed to have arteriosclerotic damage and small end vessels stiffening which can cause glaucomatous optic neuropathy. Other than that, it was also predicted that the usage of blood pressure lowering drugs can cause decreased perfusion pressure during episodic systemic hypotension (Newman-Casey et al., 2011).

In The Shihpai Eye Study conducted in Taiwan, it was found that systolic blood pressure (SBP) a positive correlation with IOP than diastolic blood pressure(DBP). It is because SBP increases aqueous humour production by ultrafiltration and consequently increases IOP. The SBP plays greater role in this than DBP. This indicates that the height of pressure wave reaching the eyes plays more important role in determining the IOP than perfusion pressure (Lin H. Y. et al., 2005). Many other studies also reported that blood pressure has a strong influence on IOP (Memarzadeh F. et al., 2008; Nomura H. et al. 1999; Rochtchina E. et al., 2002; Fukuoka S. et al., 2008). Higher blood pressure elevates IOP by not only increasing the pressure of ciliary artery and increasing aqueous humour production but also by increasing sympathetic tone and serum corticoids. Some studies suggests that more than blood pressure alone, the ocular perfusion pressure is more pertinent to development of glaucoma. Thus, suggesting that many other complex factors alongside blood pressure affect glaucoma (Choi et al., 2006; Graham et al., 2013; Bonomi et al., 2000; Leske, 2009; Caprioli & Coleman, 2010).

As stated above, a small amount of the studies implies the same results as the current study, suggesting that blood pressure has no significant relationship with NTG. However, there are more investigations that show that blood pressure does have an effect on NTG in which elevated blood pressure increases the prevalence

of NTG. Thus, further studies are needed to investigate the relationship between blood pressure and NTG to get a deeper understanding.

6.3 Limitations

There are certain limitations in this research. Although the relationship between metabolic components (fasting blood glucose level and blood pressure) and NTG is demonstrated by analyses, the cross-sectional study design limited the ability to confirm a causal relationship between these diseases. In addition, the dose-response relationship between metabolic components (fasting blood glucose and blood pressure) and NTG was not explored by the lack of details regarding severity of glaucomatous damage and metabolic syndrome.

CHAPTER 7

CONCLUSION AND SUGGESTION

7.1 Conclusions

Based on the research about relationship between metabolic components (blood pressure and fasting blood glucose level) and normal-tension glaucoma, can be concluded that:

- There is no significant correlation between blood pressure (BP) and incidence of normal-tension glaucoma.
- There is no significant correlation between fasting blood glucose (FBG) and incidence of normal-tension glaucoma (NTG).

7.2 Suggestions

Further researches are needed to be done to investigate the relationship between metabolic components (blood pressure and fasting blood glucose) and normal-tension glaucoma (NTG) because this research shows no significant relationship. Other than that, this study has certain limitations.

REFERENCES

Nakamura M, Kanamori A, Negi A. Diabetes mellitus as a risk factor for glaucomatous optic neuropathy. Ophthalmologica 2005;219:1–10.

Kanamori A, Nakamura M, Mukuno H, et al. Diabetes has an additive effect on neural apoptosis in rat retina with chroni- cally elevated intraocular pressure. Curr Eye Res 2004;28: 47–54.

Sato T, Roy S. Effect of high glucose on fibronectin expression and cell proliferation in trabecular meshwork cells. Invest Ophthalmol Vis Sci 2002;43:170–5.

Oh SW, Lee S, Park C, Kim DJ. Elevated intraocular pressure is associated with insulin resistance and metabolic syndrome. Diabetes Metab Res Rev 2005;21:434-440.

Doughty MJ, Zaman ML. Human corneal thickness and its impact on intraocular pressure measures: a review and meta- analysis approach. Surv Ophthalmol 2000;44:367–408.

European Glaucoma Prevention Study Group. Central corneal thickness in the European Glaucoma Prevention Study. Ophthalmology 2007;114:454–459.

Su DH, Wong TY, Wong WL, et al; Singapore Malay Eye Study Group. Diabetes, hyperglycemia, and central corneal thickness: the Singapore Malay Eye Study.Ophthalmology 2008;115:964–968.

Hayreh SS. Pathogenesis of optic nerve damage and visual field deficits in glaucoma. Doc Ophthalmol Proc Ser 1980;22: 89–110.

Chopra V, Varma R, Francis BA, et al; Los Angeles Latino Eye Study Group. Type 2 diabetes mellitus and the risk of open-angle glaucoma: the Los Angeles Latino Eye Study. Ophthalmology 2008;115:227–232.

Feke GT, Bex PJ, Taylor CP, et al. Effect of brimonidine on retinal vascular autoregulation and short-term visual function in normal tension glaucoma. Am J Ophthalmol 2014;158:105–112.

Flammer J, Orgul S, Costa VP, et al. The impact of ocular blood flow in glaucoma. Prog Retin Eye Res 2002;21:359–93.

Osborne NN, Melena J, Chidlow G, Wood JP. A hypothesis to explain ganglion cell death caused by vascular insults at the optic nerve head: possible implication for the treatment of glaucoma. Br J Ophthalmol 2001;85:1252–9.

Lin HY, Hsu WM, Chou P, Liu CJ, Chou JC, Tsai SY, et al. Intraocular pressure measured with a noncontact tonometer in an elderly Chinese population: The Shihpai Eye Study. *Arch Ophthalmol* 2005; 123(3): 381-386.

Memarzadeh F, Ying-Lai M, Azen SP, Varma R. Associations with intraocular pressure in Latinos: The Los Angeles Latino Eye Study. *Am J Ophthalmol* 2008; 146(1):69-76.

Nomura H, Shimokata H, Ando F, Miyake Y, Kuzuya F. Age-related changes in intraocular pressure in a large Japanese population: A cross-sectional and longitudinal study. *Ophthalmology* 1999; 106(10): 2016-2022.

Rochtchina E, Mitchell P, Wang JJ. Relationship between age and intraocular pressure:The Blue Mountains Eye Study. *Clin Experiment Ophthalmol* 2002; 30(3): 173-175.

Fukuoka S, Aihara M, Iwase A, Araie M. Intraocular pressure in an ophthalmologically normal Japanese population. *Acta Ophthalmol* 2008; 86(4): 434-439.

Klein BE, Klein R. Intraocular pressure and cardiovascular risk variables. *Arch Ophthalmol* 1981; 99(5): 837-839.

Bonovas S, Filioussi K, Tsantes A & Peponis V (2004): Epidemiological associationbetween cigarette smoking and primary open-angle glaucoma: a metanalysis. Public Health 118: 256–261.

Pasquale LR & Kang JH (2009): Lifestyle, nutrition, and glaucoma. J Glaucoma 18: 423-428.

Newman-Casey PA, Talwar N, Nan B, Musch DC & Stein JD (2011): The relationship between components of metabolic syndrome and open-angle glaucoma. Ophthalmology 118: 1318–1326.

Suh MH, Park KH & Kim DM (2009): Effect of travoprost on intraocular pressure during 12 months of treatment for normal-tension glaucoma. Jpn J Ophthalmol 53: 18-23.

Tielsch JM, Katz J, Sommer A, Quigley HA & Javitt JC (1995): Hypertension, perfusion pressure, and primary open-angle glaucoma. A population-based assessment. Arch Ophthalmol 113: 216–221.

Leske MC, Wu SY, Nemesure B & Hennis A (2002): Incident open-angle glaucoma and blood pressure. Arch Ophthalmol 120: 954–959.

Bonomi L, Marchini G, Marraffa M, Bernardi P, Morbio R & Varotto A (2000): Vascular risk factors for primary open angle glaucoma: the Egna-Neumarkt Study. Ophthalmology 107: 1287–1293.

Choi J, Jeong J, Cho HS & Kook MS (2006): Effect of nocturnal blood pressure reduction on circadian fluctuation of mean ocular perfusion pressure: a risk factor for normal tension glaucoma. Invest Ophthalmol Vis Sci 47: 831–836.

Caprioli J & Coleman AL (2010): Blood pressure, perfusion pressure, and glaucoma. Am J Ophthalmol 149: 704–712.

Graham SL, Butlin M, Lee M & Avolio AP (2013): Central blood pressure, arterial waveform analysis, and vascular risk factors in glaucoma. J Glaucoma 22: 98-103.