EVALUATION OF OPTIC NERVE HEAD PARAMETERS, RETINAL NERVE FIBER LAYER AND MACULAR THICKNESS IN METABOLIC SYNDROME

BY

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Dissertation Submitted in Partial Fulfilment of The Requirement for the Degree of Master of Medicine (Ophthalmology)

SCHOOL OF MEDICAL SCIENCES

UNIVERSITI SAINS MALAYSIA

2015

DISCLAIMER

I hereby certify that the work in this dissertation is my own except for the quotations and summaries which have been duly acknowledged.

Dated: 17 MAY 2015 …….

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ACKNOWLEDGEMENT

My sincere thanks to my supervisor, Associate Professor Dr. AzhanyYaakub, lecturer of Department of Ophthalmology, School of Medical Sciences, Universiti Sains Malaysia, Kubang Kerian for her guidance and support in the preparation of my thesis and throughout the completion of my study.

A special thanks to Professor Dr. Liza Sharmini Ahmad Tajudin, Head of Department of Ophthalmology, School of Medical Sciences, Universiti Sains Malaysia, Kubang Kerian, all lecturers and colleagues for their cooperation, assistance and encouragement.

My warmest appreciation to Dr. Zuraidah Mustari, Head of Ophthalmology Department, Hospital Sultanah Nur Zahirah for her encouragement and advice.

A special thanks to Dr. Irfan, statistician for his guidance and great tolerance. Without his help and kindness, this routine clinical works will never translate into clinical study.

To my beloved husband and my children's, thank you for the constant support and sacrifices and for always be there for me. I surely will not be as successful as today without their patience.

I hope people will be benefit from this study.

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LIST OF ABBREVIATION

MetS	Metabolic Syndrome
Non-MetS	Non Metabolic Syndrome
ONH	Optic Nerve head
RNFL	Retinal nerve fiber layer
HSNZ	Hospital Sultanah Nur Zahirah
SD-OCT	Spectral domain Optical Coherence Tomography
TD-OCT	Time domain Optical Coherence Tomography
CVD	Cardiovascular Disease
HDL	High Density Lipoprotein
WHO	World Health Organization
NCEP-ATP111	National Cholesterol Education Program-Adult Treatment Panel 111
IDF	International Diabetic Federation
NHLBI	National Heart Lung and Blood Institute
WHF	World Heart Federation
AHA	American Heart Association
IAS	International Atherosclerotic Society
BMI	Body Mass Index
BP	Blood pressure
WC	Waist circumference
IGT	Impaired Glucose Tolerance
HRT	Heidelberg Retina Tomography
SPSS	Statistical package science social
PS	Power and Sample Size

CSLO	Confocal scanning laser ophthalmoscopy
RPE	Retinal Pigment Epithelial
DR	Diabetic Retinopathy
SSI	Signal Strength Index
CDA	Cup-Disc Area ratio
CDH	Cup-Disc horizontal ratio
CDV	Cup-Disc Vertical ratio
LSRM	Lapisan Saraf Retina Mata
CSR	Central Serous Retinopathy

ABSTRAK

TAJUK

Penilaian terhadap parameter kepala saraf optik, ketebalan lapisan saraf retina mata dan ketebalan lapisan makular pada golongan yang menghidapi masalah sindrom metabolik

PENGENALAN

Sindrom metabolik merupakan kumpulan penyakit yang mempunyai kaitan dengan faktor risiko seperti obesiti, tekanan darah tinggi, gangguan insulin, gangguan lemak dan keradangan. Faktor risiko sistemik ini telah dibuktikan mempunyai pengaruh atau kesan terhadap peredaran darah mikro dan juga autoregulasi terhadap kepala saraf optik dan lapisan retina. Dengan adanya alat imaging yang terkini seperti OCT, ia telah memainkan peranan yang penting untuk membezakan rupa bentuk saraf optik, ketebalan lapisan saraf retina mata (LSRM) dan juga ketebalan lapisan makular. Oleh itu alat ini boleh digunakan untuk membuat analisa terhadap struktur-struktur ini.

OBJEKTIF

Tujuan kajian ini dijalankan adalah untuk menilai dan membandingkan parameter kepala saraf optik, ketebalan LSRM dan juga ketebalan lapisan makular dengan mengunakan alat OCT terhadap kumpulan sindrom metabolik dan bukan metabolik di kalangan kakitangan Hospital Sultanah Nur Zahirah (HSNZ).

METODOLOGI

Kajian perbandingan keratan rentas ini telah dijalankan dari 2013 sehingga 2014 bertempat di HSNZ. Sebanyak 230 sampel mata telah dipilih dalam kajian ini yang terdiri daripada 77 kumpulan sindrom metabolik dan 153 dari kumpulan bukan sindrom metabolik. Semua subjek telah menjalani pemeriksaan mata termasuk ujian ketajaman penglihatan, pemeriksaan struktur depan dan belakang mata. Penilaian parameter kepala saraf optik, ketebalan LSRM, dan ketebalan lapisan macular diambil menggunakan mesin OCT (RTVue-100).

KEPUTUSAN

Keputusan kajian mendapati bahawa kumpulan sindrom metabolik secara umumnya mempunyai bacaan nilai purata parameter kepala saraf optik yang lebih tinggi berbanding dengan kumpulan bukan sindrom metabolik kecuali di kawasan ‘disc area’ dan ‘rim area’. Manakala bagi purata ketebalan LSRM menunjukkan bacaan purata yang lebih nipis bagi kumpulan sindrom metabolik. Walaubagaimanapun tiada perbezaan yang signifikan bagi semua variasi bagi kedua-dua kumpulan. Kumpulan sindrom metabolik menunjukan nilai bacaan purata lapisan makular yang lebih tinggi kecuali dibahagian ‘inferior hemisphere’, ‘superior’ dan ‘inferior’ kawasan parafovea. Lebih spesifik lapisan makular bagi kumpulan metabolik menunjukkan perbezaan yang signifikan berbanding bukan metabolik dibahagian ‘temporal parafoveal’ 304.45(16.61); 293.88(18.82) dengan nilai $p < 0.001$, ‘inferior hemisphere of perifovea’ 288.10(23.62); 280.09(22.25) dengan nilai $p=0.013$ dan ‘temporal perifovea’ 289.57(21.85); 277.23(21.90) dengan nilai $p < 0.001$).

KESIMPULAN

Sindrom metabolik memberi kesan yang signifikan terhadap ketebalan makular di bahagian ‘inferior hemisphere of perifoveal’, ‘temporal part of parafoveal’ dan ‘temporal part of perifoveal’. Walau bagaimanapun ia tidak memberi kesan terhadap perubahan pada kepala saraf optik dan LSRM.

ABSTRACT

TITLE

Evaluation of optic nerve head parameters, retinal nerve fiber layer, and macular thickness in metabolic syndrome

INTRODUCTION

Metabolic Syndrome (MetS) denotes a common cluster of naturally connected risk factors including obesity, elevated blood pressure, insulin resistance, dyslipidaemia, proinflammatory state and prothrombotic state. This systemic risk factor are proved to have influence on microcirculation and blood flow autoregulation of the optic nerve head (ONH). The recent availability of retinal imaging such as optical coherence tomography (OCT) play an important role to differentiate the appearance of optic nerve head (ONH), retinal nerve fiber layer (RNFL) and macular thickness and therefor can be used for macular and optic nerve analysis.

OBJECTIVES

This study aim is to evaluate ONH parameters, RNFL and macular thickness using RTVue-100 Fourier domain OCT in MetS and Non-MetS group among Hospital Sultanah Nur Zahirah (HSNZ) staffs.

METHODOLOGY

A comparative cross sectional study was carried out from Mac 2013 till October 2014 in Hospital Sultanah Nur Zahirah. A total of 230 eyes was included in this study (one eye from each of 230 subjects) in which 77 eye from MetS and 156 eye from Non-MetS group and were compared between this groups. All subjects underwent ophthalmologic examination including visual acuity, anterior and posterior segment examination. An assessment of ONH parameters, RNFL and macular thickness in 4 quadrant was conducted using RTVue-100 OCT.

RESULTS:

The result showed MetS group generally have higher value of ONH parameters as compared to Non-MetS group with exception of two ONH parameters; disc area and rim area. Meanwhile for the RNFL parameter thickness generally showed thinner mean value in MetS group. However there were no statistically significant difference seen between MetS and Non-MetS for both parameters. Whereas macular parameter thickness result showed MetS group had thicker mean value compared to Non-MetS group with exception of inferior hemisphere, superior and inferior quadrant of parafovea subareas. More specifically, macular thickness were significantly thicker in MetS than Non-MetS in the temporal quadrant of parafoveal, 304.45(16.61); 293.88(18.82) with p value <0.001, inferior hemisphere of perifovea 288.10(23.62); 280.09(22.25) with p value 0.013 and temporal quadrants of perifovea 289.57(21.85); 277.23(21.90) with p value <0.001.

CONCLUSION:

MetS significantly affect macular thickness at the temporal part of parafovea area, temporal and inferior hemisphere of perifovea area, but not affect the ONH parameters and RNFL.

ABSTRACT

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INTRODUCTION: Metabolic Syndrome (MetS) denotes a common cluster of naturally connected risk factors including obesity, elevated blood pressure, insulin resistance, dyslipidaemia, proinflammatory state and prothrombotic state. This systemic risk factor are proved to have influence on microcirculation and blood flow autoregulation of the optic nerve head (ONH). The recent availability of retinal imaging such as optical coherence tomography (OCT) play an important role to differentiate the appearance of optic nerve head (ONH), retinal nerve fiber layer (RNFL) and macular thickness and therefor can be used for macular and optic nerve analysis.

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CONCLUSION: MetS significantly affect macular thickness at the temporal part of parafovea area, temporal and inferior hemisphere of perifovea area, but not affect the ONH parameters and RNFL.

Associate Professor Azhany Yaakub: Supervisor

Professor liza Syamimi Tajudin : Co-Supervisor

CHAPTER ONE

1.0 INTRODUCTION

1.1 Overview of the study

Many diseases affecting the retina and optic nerve are leading causes of vision loss in adult. Studies suggest that these ocular condition may have a vascular in aetiology (Cheung *et al.,* 2008; Wong *et al.,* 2001). Diabetes mellitus is known to cause microvascular damage and may affect vascular auto regulation of the retina and optic nerve and has been found to be associated with elevated intraocular pressure (Dielemans *et al.,* 1996; Klein BE *et al.,* 1992).

Metabolic Syndrome (MetS) is one type of metabolic abnormalities. It also has microvascular effect. However, up till there is still no study done to evaluate the changes in the ONH parameters, RNFL and macular thickness among MetS. Many studies were done that showed other factors that contribute to the retina and optic nerve changes such as age, gender, ethnicity, axial length, refractive error and optic nerve diseases (O'Rese *et al.*, 2012; Girkin *et al.*, 2011).

1.1.1 MetS

The combination of metabolic disturbances now known as the MetS was first described by Kylin in the 1920s as the clustering of hypertension, hyperglycaemia and gout. Two decades later, Vague *et all* in 2008 reported that upper body adiposity (android or male-

type obesity) was the type most often associated with the metabolic abnormalities seen with diabetes and cardiovascular disease (CVD).

During the 1988 Banting Lecture, Reaven used the term ‘Syndrome X’ and firmly established the clinical importance of this syndrome, although obesity was not included. In 1989, Kaplan renamed it ‘The Deadly Quartet’ and others then coined the term ‘The Insulin Resistance Syndrome’. It is now agreed that the well-established term ‘metabolic syndrome’ remains the most useful and widely accepted description of this cluster of metabolically related cardiovascular risk factors which also predict a high risk of developing diabetes (if not already present).

MetS is a condition characterized by the presence of at least 3 of the following: abdominal obesity, increased blood pressure (BP), impaired glucose tolerance (IGT) or diabetes, dyslipidaemia (elevated levels of triglycerides (TG) and low concentration of high-density proteins (HDL). Other abnormalities have also been reported including the presence of pro-inflammatory and prothrombotic state by Rasic *et al* in 2007 as well as an altered oxidative / antioxidant ratio by Aldini *et al* in 2007. The increase in oxidative stress markers is proportional to the number of risk factors for the MetS which are present.

There are several widely accepted definitions of MetS (Table 1.1). They have been issued by the National Cholesterol Education Program/Adult Treatment Panel III (NCEP-ATP III), World Health Organization (WHO) and the International Diabetes Federation (IDF). They differ slightly in criteria of diagnosis of the MetS. The third

definition underlines for the first time the importance of abdominal adiposity as a risk factor for the development of MetS.

Recently, a unified MetS definition prepared by the IDF, National Heart, Lung and Blood Institute, World Heart Federation, the International Atherosclerosis Society and the American Heart Association has been published in order to eliminate confusion regarding the identification of patients with MetS. The differences in the diagnostic criteria lead to a joint interim statement to harmonize the MetS definition. The common definition agrees that abdominal obesity should not be the prerequisite. They proposed that diagnosis should be based on entirely on the presence of any 3 out of 5 risk factor as the basis for establishing diagnosis and they proposed "Harmonised criteria"

Subjects with MetS are at higher risk of developing atherosclerotic, cardiovascular disease, risk of renal injury, sleep-disordered breathing and development type 2 diabetes compared with those without the syndrome (Satar *et al.,* 2007). Characteristic of large and small vessel disease such as inflammation and endothelial dysfunction also have been reported by Satar *et al* in 2007 to be associated with MetS. The uneven production of pro and anti-inflammatory cytokines leads directly to atherosclerosis (Greenberg *et al.,* 2002; Gaal *et al.,* 2006).

It is also suggested that type 2 diabetes and atherosclerotic vascular disease have shared pathogenetic pathways in which insulin resistance and abdominal obesity play a central role. Study done by Wassink *et al* in 2008 reported presence of MetS was associated with 4-6 fold increased risk of future type 2 diabetes. This finding indicates that in a cohort of patients at high risk of future type 2 diabetes, metabolic syndrome is able to identify those at the highest risk.

Table 1.1 Definition of Metabolic syndrome according to different criteria.

Risk Factors	**WHO (1999)**	**NCEP-ATP III (2001)**	**IDF (2005)**	**Harmonized criteria (2009)**
Obesity (BMI) or Waist Circumference (WC)	BMI ≥ 30kg/m2 and / or WHR > 0.9 [M] > 0.85 [F]	WC [Caucasian] M ≥ 102 cm F ≥ 88 cm	WC [Asian] M ≥ 90cm F ≥ 80 cm	WC [Asian] M ≥ 90cm F ≥ 80 cm
High BP (Systolic/Diastolic)	≥ 140/90 mmHg or on treatment	≥ 130/ 85 mmHg	≥ 130/85mmhg or on treatment	≥130/85 mmHg or on treatment
High FPG (mmol/l)	DM, IGT or IR	≥ 6.1 or DM	≥ 5.6 or DM	≥ 5.6 or DM
Microalbuminuria	≥ 20µg/min or ACR ≥ 30 mg/g	Not used	Not used	Not used
Elevated TG	≥ 1.7 mmol/l	≥ 1.7 mmol/l	≥ 1.7 mmol/l	≥ 1.7 mmol/l
Reduced HDL-C	< 0.9mmol/l [M] < 1.0mmol/l [F]	< 1.03mmol/l [M] < 1.29mmol/l [F]	<1.03mmol/l[M] <1.29mmo/l [F]	<1.0mmol/[M] <1.3mmo/l[F]
Metabolic Syndrome	**DM, IGT or IR + any 2 or more risk factor**	**At least 3 risk factor**	**WC + 2 or more risk factor**	**At least 3 risk Factor**

WHO: World Health Organization; NCEP-ATP III: National Cholesterol Education Program/Adult Treatment Panel III; IDF: International Diabetes Federation; IGT: Impaired Glucose Tolerance; WC: Waist circumference; IR: Insulin Resistance; ACR: Albumin Creatinine ratio; FPG: Fasting Plasma Glucose; WHR: waist hip ratio.

The association of individual component of MetS with retinopathy, cataract and raised intraocular pressure is well known. However, to the best of our knowledge, there was no study conducted in MetS population in relation with ONH, RNFL and macular thickness.

Little is known on the prevalence of MetS in Malaysia. This syndrome is increasingly being recognised as a distinct entity affecting a large proportion of US adult population. A small survey by Tan *et al* in 2008 on prevalence of Mets among Malaysian involving 109 adults done in Malaysia, reported a prevalence of 22.9% and 16.5% by IDF and ATP III definitions, respectively while a hospital-based study by Termizy *et al* in 2009 recorded a 40.4% prevalence among patients attending an obesity clinic.

A first nationwide survey conducted by Mohamud *et al* (2011) in prevalence of MetS and its risk factors in adult Malaysians based on the WHO, ATP 111, IDF and Harmonised criteria definition, the overall crude prevalence of MetS were 32.1%, 34.3%, 37.1% and 42.5% respectively. Regardless of the criteria used, MetS was higher in urban areas, in females (43.7%), in the Indians population (51.9%) and increased significantly with age. The Malays and Chinese population are 43.9% and 42.1% respectively. They found that Malaysia has a much higher prevalence of MetS compared with other Asian countries such as India (Deepa *et al*.,2007), Hong Kong (Ko *et al*.,2006) and China (Gu *et al*.,2005) where prevalence ranged from 6.1 to 18.3%.

Many others studies have shown that the prevalence of MetS varies among different ethnic populations living in the same countries and is postulated to be associated with environmental and genetic factors (Poulsen *et al.*, 2001; Reilly *et al.*, 2003). Local

survey done in Hospital Sultanah Nur Zahirah in 2011, the unpublished data showed the prevalence of MetS among staffs using Harmonised criteria was 21.42%.

1.1.2 Retinal microvascular associations of MetS

Characteristics of large and small vessel disease such as inflammation and endothelial dysfunction have been reported by Duncan *et al* in 2003 to be associated with MetS and its component. Recent studies have shown that these retinal vascular signs are associated with systemic markers of inflammation and endothelial dysfunction (Klein *et al.,* 2000; Wong *et al.*,2006; Ikram *et al*.,2004). It has been speculated that retinal venular widening are reflect of inflammatory processes implicated in the pathogenesis of impaired glucose metabolism.

In a population-based cross-sectional study by Wong *et al* in 2004 involving 11,265 persons, retinal photographs were taken and graded for the presence of retinal microvascular signs. The data showed that persons with MetS were significantly more likely to have retinopathy, arteriovenous nicking, focal arteriolar narrowing, smaller retinal arteriolar diameters, and larger retinal venular diameters than people without the syndrome, independent of age, gender, race, education, cigarette smoking, and alcohol consumption. With the exception of retinopathy, most associations were significant even in people without diabetes or hypertension, suggesting that factors other than hyperglycemia and high BP (i.e. dyslipidemia, obesity, and inflammation) may explain the occurrence of these retinal lesions.

In another study done by Kawasaki *et al* in 2008 conducted among Japanese adults, the various components of the MetS were found to be associated with retinal microvascular signs: a larger waist circumference was associated with wider venular diameter and retinopathy lesions; a higher BP level was associated with focal arteriolar narrowing, arteriovenous nicking, enhanced arteriolar wall reflex, and narrower arteriolar diameter; and a higher TG level was associated with enhanced arteriolar wall reflex. Overall, persons with the MetS were more likely to have retinopathy (odds ratio 1.64, 95% CI: 1.02–2.64) and wider venular diameter of 4.69 μm (95% CI: 1.20–8.19 μm) than persons without the MetS in this study.

The association between MetS and retinopathy was also studied in persons 40 years of age and older with gradable fundus photographs in the National Health and Nutrittional Examination Survey III database (NHNES 111). However in this population-based cross-sectional study, there was no evidence of an association between the MetS and retinopathy independent of diabetic status (Keenan *et al*., (2009).

Obesity, one of the major components of MetS, has been shown to be associated with retinopathy signs in the general and non-diabetic population (Cheung *et al.,* 2007). In the Hoorn Study in the Netherlands, waist–hip ratio was independently associated with a number of incident retinopathy signs including retinal haemorrhages, microaneurysms, hard exudates, and cotton wool spots in the non-diabetic general population, although the association with body mass index (BMI) failed to achieve a statistical significance (Leiden *et al.,* 2003)

1.1.3 ONH morphology

The ONH represent an area of considerable specialization where axons from retinal ganglion cells leave the eye (Lawrenson *et al*., 2007). It forms bundles that constitute the nerve fiber layer, which converges like spokes of wheel at the ONH. The ONH is about 1 mm long and its diameter is 1.5 mm horizontally, 1.8mm vertically at the level of the retina and little wider in the retrolaminar space.

It is major zone of transition, because nerve fibers pass from an area of high tissue pressure within the eye to a zone of low pressure that correlates with intracranial pressure. At the same time the nerve fibers leave an area in which their blood supply is from the central retinal artery alone to zones supplied by other branch of ophthalmic artery. The blood supply to the ONH derives from the circle of Zinn-Haller which forms a ring about it. It quantitative measurement and analysis is essential to distinguish a normal from abnormal optic disc.

1.1.4 Variation in ONH parameters

The measurement of stereotric parameters of ONH has been done using many techniques including optical coherence tomography (OCT), Heidelberg retina tomography (HRT), scanning laser polarimetry etc. They quantify the nerve fiber layer of disc and surrounding retina and statistically correlate the findings with a database of previously screened population of normal. They are useful for baseline and serial follow-up to monitor minute changes in optic disc morphology. Imaging will not

provide conclusive evidence for clinical diagnosis however, and the evidence needs to be supplanted by serial physiological testing for functional changes.

1.1.5 RNFL

RNFL is a packed between the inner limiting membrane and the retinal ganglion cell layer. In normal eyes, the RNFL is usually best visible in the inferior temporal part of the fundus, followed by the superior temporal region, the nasal region and the nasal inferior region (Jonas *et al.*, 1996). As ONH there are several devices that can be used to analyse the RNFL such as OCT, HRT, confocal scanning laser ophthalmoscopy (CSLO), and scanning laser polarimeter (GDx nerve Fiber Analyser).

1.1.6 Macular morphology

Macular thickness changes are commonly seen in eyes with retinal pathologies, such as macular thickening or oedema from age-related macular degeneration, diabetic retinopathy (DR), retinal vein occlusion, and uveitis; and macular thinning or atrophy caused by cell loss occurs in retinal dystrophies and also seen in glaucoma. Evidence has shown that the degree of macular thickening and macular thinning is correlated with visual function; therefore, knowledge of normal macular thickness provides a benchmark for evaluating pathologic macular changes.

Traditional methods for evaluating macular pathology, such as slit lamp biomicroscopy, stereoscopic photography, and fluorescein angiography, are relatively insensitive to small changes in retinal thickness and are qualitative at best. OCT is now commonly used to measure macular thickness quantitatively for disease diagnosis and to monitor

the efficacy of therapeutic modalities. OCT measurements of macular thickness have been demonstrated to be highly reliable. However, there are limited data of normal macular thickness, with most studies conducted from clinic-based samples.

1.1.7 Variation of ONH parameters, RNFL and macular thickness

Differences in ONH parameters, RNFL and macular anatomic features have been demonstrated between age, racial groups, gender, axial length and refractive error which may have an effect on the detection of certain disease such as glaucoma.

Histopathologic studies of ONH and RNFL in adults and children have shown decrease nerve fiber count with increasing age and demonstrated statically significant inverse correlation between age and axon count in normal optic nerves (Balazsi *et al*,. 1995; Jonas *et al.,* 1992). They also had found a visibility of the RNFL with age. They correlated this finding with an age-related of the optic nerve fiber which is about 4000-5000 annual losses of fibers per-year. Thus the morphology of the optic disc may change with age due to reduction of optic nerve axons and nerve fiber layer.

A study done by Pang *et al* in 2009 on normal parameters of African American children age 6-17 years had found only cup-to-disc area ratio and linear cup-to-disc area ratio that had significant differences between genders. They had reported these two parameters were greater in boys than in girls.

Studies conducted by Budenz *et al* in 2005 to determine the effects of age, optic disc area, ethnicity, eye, gender, and axial length on the RNFL in the normal eye concluded

that RNFL thickness, as measured by OCT, varies significantly with age, ethnicity, axial length, and optic disc area. Similar result was also shown by a study done by O'Rese *et al* in 2012 on effect of race, age, axial length on ONH parameters and RNFL thickness measured by OCT.

However there are studies which reported that no age related differences were detected on ONH parameters and RNFL thickness of normal eyes. Pang *et al* in 2009 had analysed 146 African American children age 6-17 years on normal eyes and reported no significant differences on ONH parameters detected on these children. Salchow *et al* in 2006 had performed a study on 92 normal children ages 4 to 17 year and found that there was no significant difference in RNFL thickness between genders.

1.2 ONH parameters, RNFL and macular thickness imaging

1.2.1 OCT

OCT is an axial cross–sectional imaging of tissue based on the back scattering of low-coherence laser light (850nm) as it pass through layers of differing optical density. The physical principles of OCT are similar to those of ultrasound, although OCT has much higher resolution. The back scattering of the stimulus light beam as it transitions from one layer (e.g., nerve fiber layer) to another (retinal ganglion cells) is recorded by an interferometer and amplified to construct a 2-dimentional image of the scanned area. The procedure is non-contact and non-invasive.

1.2.2 Time Domain and Spectral Domain OCT

The two type of OCT that available are Time Domain OCT (TD-OCT) and spectral Domain OCT (ST-OCT). The SD-OCT gives more advantage which provides significant increase in image acquisition speed, resolution and sensitivity (Keane et al., 2011).

TD-OCT is available since 2002. It was rapidly being used as a standard for posterior segment retinal tomography. The diode light source (843) is split into 2 perpendicular beams as one is directed for reference arm and the other source enter the patient's eye. The reflected light from the two paths form an interference pattern and due to coherent detection the reflecting retinal layers can be measured.

The detail reflecting is constructed into the retinal thickness map. Description of the different intraretinal layers in OCT image has been publishing in detail. However several different studies shown sensitivity and specificity of TD-OCT in detecting early glaucoma has been found to be only moderate to high (Garas *et al*.,2010). The recently developed Fourier-domain OCT technology provides better outcomes.

SD-OCT also called Fourier –Domain OCT system is the fourth generation of OCT which is the latest, have made high resolution, easier clinical application and fast scanning speed possible. The resolution being up to five times higher and imaging speed up to 60-65 times faster than conventional TD-OCT. In comparison to the TD-OCT, it is able to handle and analyse complex data for three dimensional image reconstructions. It gives better resolution for delineation of pathology and better retinal coverage with increased imaging depth. It also able to eliminate the motion artefact (Sinha *et al*., 2011). However, published information from clinical studies on the reproducibility and diagnostic accuracy of this technology is limited.

1.2.3 HRT

HRT is a confocal scan laser device from Heidelberg Engineering that provides precise topographic maps of the optic disc and the peripapillary retina. It yields papillary morphometric parameters at the global level and for each of the six sectors in which the papilla is divided. It also has diagnostic classifications such as the Moorfield Regression or the Glaucoma Probability Score, and follow-up analysis tools such as the Topographic Change Analysis.

1.3 Rationale of the study

Differences in ONH parameters, RNFL and macular anatomic features have been demonstrated between age, racial groups, gender, axial length and refractive error. Some of the systemic disease such as diabetes mellitus and glaucoma are well known diseases that cause changes in this parameters as the disease progress (Oh *et al*., 2005)

Kawasaki *et al* observed that individual with MetS were more likely to have retinopathy and wider venular diameter. Similar observation also found in population-based cross sectional study where the data showed persons with MetS were significantly more likely to have retinopathy, arteriovenous nicking, focal arteriol narrowing, smaller retinal arteriol diameters, larger retinal venular diameters than people without syndrome (Wong et al., 2004). However, there is still lacking of information either individuals with MetS also having changes in their ONH parameters, RNFL and macular thickness as compared to control.

This study was aimed to compare all these parameters with the control. The findings obtained from this study hopefully able to benefit the clinician in management of patients, early recognition and intervention.

CHAPTER TWO

2.0 OBJECTIVES

2.1 General objectives

To evaluate the ONH parameters, RNFL and macular thickness in MetS among Hospital Sultanah Nur Zahirah staffs.

2.2 Specific objectives

1. To compare the mean of ONH parameters between MetS and Non-MetS
2. To compare the mean of RNFL parameters thickness between MetS and Non-MetS.
3. To compare the mean of macular thickness between MetS and Non-MetS.

CHAPTER THREE

3.0 METHODOLOGY

3.1 Research design

Type of study : Comparative cross sectional study

3.2 Sampling frame

Study population : All hospital staffs

Place of the study : Hospital Sultanah Nur Zahirah, Kuala Terengganu, Terengganu

Period of study : March 2014 – December 2014

3.3 Selection criteria

3.3.1 Inclusion criteria for MetS

- All staffs age from 20-60 years old
- Fullfils the Harmonised criteria (Table 1.1)
- Good quality of OCT images with Signal Strength Index >30

3.3.2 Exclusion criteria for MetS

- Optic nerve disease such as glaucoma, atrophy, papilloedema, disc hemorrhage
- Media opacity which interfering the fundal view
- Retinal diseases such as diabetic retinopathy, hypertension (>grade 1), retinitis pigmentosa and staphyloma

- Macular disease such macular scar, central serous retinopathy and macula hole
- Refractive error (myopia > -3.00, hyperopia > +3.00)

3.3.3 Inclusion criteria for Non-MetS

- All staffs age from 20-60 years old
- Good quality of OCT images with Signal Strength Index > 30

3.3.4 Exclusion criteria for Non-MetS

- Optic nerve diseases such as glaucoma, atrophy, papilloedema, disc hemorrhage
- Media opacity which interfering with fundal view
- Retinal diseases such as diabetic retinopathy, hypertension (>grade 1), retinitis pigmentosa and staphyloma
- Macular diseases such as macular scar, central serous retinopathy and macula hole
- Refractive error (myopia > -3.00, hyperopia > +3.00)

3.4 Sampling and sample size

3.4.1 Sampling method

All Kementerian Kesihatan Malaysia hospital staffs especially those 40 years old and above are compulsory to do yearly health screening. The data from year 2012 was taken and staffs were divided into two groups MetS group based on Harmonised criteria and

Non-MetS. Then probabilities sampling which were simple random sampling methods were used for each group. Those who had fullfiled study criteria were recruited in this study.

3.4.2 Sample size calculation

Sample size was calculated using PS (power and sample size) software. Calculation was made using independent t-test for objective 1 to 3. The statistical parameters used were as below:

- $\alpha = 1.96$ for $\alpha = 0.05$ (two tailed),
- $\beta = 0.84$ for 80% power of study
- σ = Standard Deviation or SD
- $\delta = \Delta$ = Detectable difference or DD = the smallest clinically meaningful difference in parameter normal population.
- m = ratio between groups

3.4.2.1 For objective 1

To compare mean ONH parameters between MetS and Non-MetS group.

(Mean C/D area ratio in normal population)

Formula: independent t test

- $\alpha = 1.96$ for $\alpha = 0.05$ (level of significant)
- $\beta = 0.84$ for 80% power of study
- σ or SD = 0.18 (ref: Li *et al*.,2010)
- δ or DD = 0.09

- m = 2.11
- n = 70 and control subject group: 140
- n = 70 + (10% dropped out) = 77,

  = 140 + (10% dropped out) = 153

3.4.2.2 For objective 2

To compare mean RNFL thickness between MetS and Non-MetS.

(Mean average thickness in normal population)

Formula: independent t test

- $\alpha = 1.96$ for $\alpha = 0.05$
- $\beta = 0.84$ for 80% power of study
- σ or SD = 11.288 (ref: Li. *et al*.,2010)
- δ or DD = 5.64
- m = 2.11
- n = 70 and control subject group: 140
- n = 70 + (10% dropped out) = 77,

  = 140 + (10% dropped out) = 153

3.4.2.3 For objective 3

To compare mean macular thickness between MetS and non-MetS

(mean fovea thickness in normal population)

Formula: independent t test

- $\alpha = 1.96$ for $\alpha = 0.05$
- $\beta = 0.84$ for 80% power of study
- σ or SD = 15 (ref: Sull *et al.*, 2010)
- δ or DD = 7.5
- m = 2.11
- n = 70 and control subject group: 14
- n = 70 + (10% dropped out) = 77,

  = 140 + (10% dropped out) = 153

Final sample size base on calculation was 77 for MetS and 153 for Non-MetS.

3.5 Ethical approval

This study was approved on 3rd March 2014 by Human Research Ethics Committee, School of Medical Sciences, Universiti Sains Malaysia with certificate number USMKK/PPP/JEPeM/275.3. (11), FTW Reg. No: 00007718; IRB Reg. No: 00004494. This study also was approved by ethical & Medical Research Committee of Ministry of Health, Malaysia on 3rd November 2013 with registration number of NMRR -13-1416-17945.

3.6 Definition of terms

3.6.1 MetS

MetS is a multiplex risk factor that arises from insulin resistance accompanying abnormal adipose deposition and function. It is a risk factor for coronary heart disease, as well as for diabetes, fatty liver, and several cancers. Its consist cluster of diseases including central obesity, dyslipidaemia, hyperglycaemia, and high BP. Base on Harmonised Criteria at least 3 risk factor of the following:

1) Abdominal obesity (WC) M = 90 cm, F = 80 cm

2) High BP (systolic/diastolic) 130/85 mmHg or on treatment

3) High FPG (mmol/L) > 5.6 or Diabetic Mellitus on treatment

4) Elevated TG >1.7 mmol/L

5) Reduced HDL-C <1.0 mmol/L (M), <1.3 mmol/L (F)

3.6.2 RTVue-100 (version 3.0) OCT

The Optovue RTVue-100 (Optovue, Inc, Fremont, CA, USA) OCT used in this study is a newer version of OCT based on spectral domain technology that provide higher resolution and faster scanning that acquire images at 26000 A-scan per second, a 65-fold improvement and has an axial resolution of 5 μm. The RTVue-100 uses a scanning laser diode with a wavelength of 830 nm and can image both anterior and posterior segments of the eye. In the posterior segment, this OCT excels in quantitative analysis of retinal and optic nerve images for both retinal diseases and glaucoma. In the

anterior segment, the RTVue offer unprecedented resolution and speed for corneal and angle imaging.

3.6.3 ONH parameters

The ONH represent an area where axon from retinal ganglion cell leaves the eye. The optic cup was defined automatically by RTVue software as the intersection points of the nerve head inner boundary and a parallel line that is 150 mm above the connecting line of the RPE tips. The ONH scan is combination of circular scans for RNFL thickness analysis and radial scans for ONH shape analysis. Combining 13 circular lines with diameters of 1.3-4.9 mm and 12 radial lines with 3.7 mm length into one single pattern ensures that the RNFL scan and ONH scan naturally share same centre.

ONH parameters obtained were optic disc area, cup area, rim area, rim volume, nerve head volume, and cup volume, cup-to-disc area ratio, cup-to-disc horizontal ratio, and cup-to-disc vertical ratio, RNFL average thickness

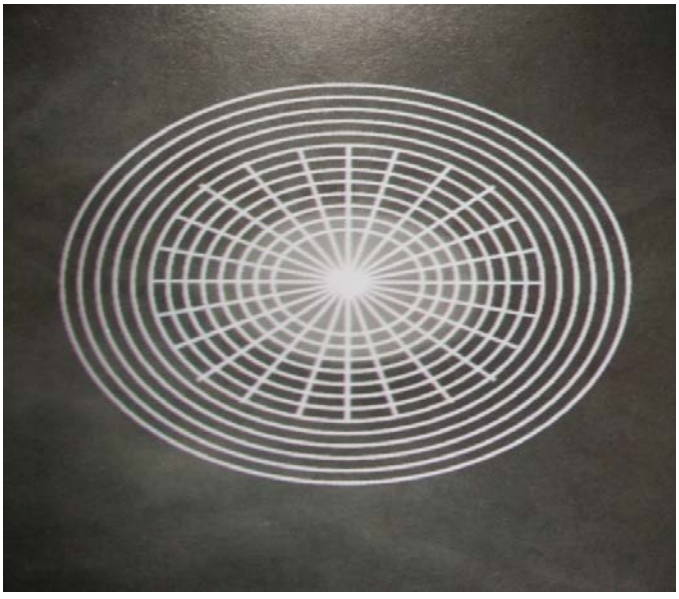

Figure 3.1 The ONH scan pattern. The 13 circular B scan range in diameter from 1.3 mm - 4.9 mm and the radial B scan are 3.7 mm in length.

3.6.3.1 Disc Area

It is the area pertaining to ONH. The margin is defined as the inner edge of the scleral, defined by a dense fibrous tissue, the Elschnig's ring.

3.6.3.2 Cup Area

Cup area is a cup shape depression of optic nerve head where the central retinal vessels entered and leave the eye. The physiological cup is located slightly temporal to its geometric centre (Snell and Lemp, 2007).

3.6.3.3 Rim Area

Area of neuroretinal rim around the central depress area of the ONH. It is the edge of the optic disc which is flat and very slightly raised (Snell and Lemp, 2007).

3.6.3.4 Rim Volume

The volume of the neuroretinal rim. Volume is enclosed by contour line and is located above the reference plane.

3.6.3.5 Nerve head volume

Volume of the optic nerve head.

3.6.3.6 Cup volume

Volume of the optic disc cup. An increase value indicate glaucomatous changes.

3.6.3.7 Cup-Disc Area ratio (CDA)

It is defined as ratio between central depress area of ONH with diameter of the ONH.

3.6.3.8 Cup-Disc Horizontal ratio (CDH)

Is defined as ratio between central depress area of optic nerve head with horizontal diameter of the ONH.

3.6.3.9 Cup-Disc Vertical ratio (CDV)

Is defined as ratio between central depress area of optic nerve head with vertical diameter of the ONH.

3.6.4 RNFL thickness

The thickness profile of RNFL at calculated 3.45-mm diameter radius around the centre of disc. Circular scans around the ONH capture RNFL measurement of the peripapillary region according to the distance between inner nerve fiber layer and outer Plexiform Layer.

Analyses provide comparison of measurements to a normative database, demonstration of asymmetry and serial analysis. The measurements were described as average RNFL and RNFL in the inferior, temporal, superior, and nasal quadrants. The RNFL thickness