THE EFFECT OF ATORVASTATIN ON MACULAR PIGMENT OPTICAL DENSITY (MPOD)

AYE CHAN SU SU

MASTER OF SCIENCE
IN
ANTI-AGING AND REGENERATIVE MEDICINE

SCHOOL OF ANTI-AGING AND REGENERATIVE MEDICINE
MAE FAH LUANG UNIVERSITY
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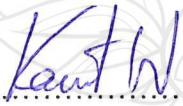

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ABSTRACT

Serum lipoproteins such as LDL and HDL cholesterol are part of the transport mechanism of lutein and zeaxanthin to the retina to serve as macular pigment. Macular pigment optical density is one of the best indicators of retinal disease such as age-related macular degeneration. Thus, this study intends to investigate the effect of Atorvastatin used in treating hypercholesterolemia on macular pigment value. This is a cross-sectional analytical study. Forty-four patients of Asian male and female, within 30-60 years of age, residing in Thailand are divided into two equal groups. The patients taking Atorvastatin 10mg for at least 6 months are placed in the study group and compared with the normal patients who are not taking medication. The macular Pigment density of each group is measured using Macular Pigment Screener II. All participants are required to sign the informed consent and complete the questionnaire regarding various factors that may influence the MPOD value. The mean MPOD of the study group who are taking Atorvastatin 10mg for at least 6 months is 0.3295 ± 0.1311 d.u. and the mean MPOD of the normal control group is 0.4686 ± 0.1491 d.u. The results showed that the mean MPOD of the study group is significantly lower than the

control group (p = 0.002). In conclusion, the patients taking Atorvastatin have lower MPOD value than normal people.

Keywords: Macular Pigment Optical Density, Hypercholesterolemia, LDL Cholesterol, HMG CoA Reductase Inhibitor, Atorvastatin

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CHAPTER 1

INTRODUCTION

1.1 Background

Hypercholesterolemia is regarded as one of the most common metabolic disorders, which is increasing in prevalence all over the world. It is a form of dyslipidemia that indicates an increased level of low-density cholesterol (LDL-C) in the serum. The National Health and Nutrition Examination Survey done in 2003-2006 stated that 53% of the adult population in the United States have abnormal serum lipid levels. Comparing to other middle-income countries in Asia, Thailand was reportedly amongst one of the countries with the highest unawareness rate regarding hypercholesterolemia at 78% in 2004, with a low level of treatment and control (Narindrarangkura, Bosl, Rangsin & Hatthachote, 2019).

Increased cholesterol in the blood raises the risk of atherosclerotic and cardiovascular disease, cerebrovascular accidents, and type 2 diabetes mellitus. It is the major cause of disease burden in both developed and developing countries. It is estimated to attribute to 4.5% of total deaths and 2% of total DALYS according to Global Health Observatory (GHO) data. There are several studies regarding the relationship between oxidative stress in hypercholesterolemia. It is proved that there is an increased total cholesterol pool in cells causing lipid peroxidation which leads to the altered cell membrane of the cells, increased oxidative stress on the cells, elevated level of reactive oxygen species (ROS), and decreased level of antioxidant enzymes all over the body (Singh, Kumar & Dhakal, 2017).

Age-related macular degeneration (AMD) is regarded as one of the major causes of irreversible visual loss in the elderly (Bellezza, 2018). Risk factors for AMD involve Genetics, Ethnicity, Aging, and Environmental factors including high cholesterol, smoking, and photo-oxidative reactions (Organisciak & Vaughan, 2010). Aging,

hypercholesterolemia, smoking, and photo-oxidative reactions mainly contribute to the production of ROS and the promotion of oxidative stress.

Macular pigment (MP) protects the retina by absorbing harmful short-wavelength blue light in the inner retina and acting as scavengers in the photoreceptors. Macular pigment is mainly located in the fibers of Henle in the fovea site and the inner part of the nuclear layer at the parafoveal site. The main components of the macular pigment include carotenoids such as lutein, xanthin, and zeaxanthin (Bone, Landrum, Hime, Cains & Zamor, 1993). The carotenoids are accountable for the coloration of the yellow macula lutea and provide the retina with antioxidant properties. (Beatty, Boulton, Henson, Koh, & Murray, 1999; Bone et al., 1993). Macular Pigment Optical Density or MPOD is the measurement of the level of macular pigment density in the retina which absorbs and reduces the damage caused by blue light and is directly related to the amount of lutein and zeaxanthin in the macula. MPOD is usually presented with Optical density levels or density units (d.u). Optical density levels in the center of the macula vary from 0 to 1 (Bone, Landrum & Cains, 1992). The study described that the average MPOD value of the South East Asians is at 0.43 d.u (Howells, Eperjesi & Bartlett, 2013).

There are various means to measure MPOD such as psychophysical and optical. These include heterochromatic flicker photometry (Delori, Goger, Hammond, Snodderly & Burns, 2001), minimum motion photometry (Robson et al., 2005), imaging reflectometry, and Raman spectrometry (Elsner, Burns, Beausencourt & Weiter, 1998; Bernstein et al., 2002), reflectometry (Berendschot, Willemse-Assink, Bastiaanse, de Jong, & van Norren, 2002) and autofluorescence spectrometry (Delori et al., 2001). Among those methods, one of the most widely used techniques is heterochromatic flicker photometry (HFP). In this study, the MPOD levels will be measured using Macular Pigment Screener II (MPS II) which is one of the recently introduced instruments using HPF technology. Moreover, serum lipid profile and glycosylated haemoglobin (HbA1C) levels will be measured to correlate with the measured MPOD values.

HMG CoA reductase inhibitors, commonly known as statins are drugs mainly used in the treatment of hypercholesterolemia. They decrease endogenous cholesterol synthesis and reduce the serum level of LDL cholesterol in the blood. There is a significant protective effect of statins on AMD in the elderly which may be due to their secondary action such as anti-inflammatory, antioxidant, and anti-thrombotic effects

(Roizenblatt, Naranjit, Maia & Gehlbach, 2018). This class of drugs includes simvastatin, atorvastatin, rosuvastatin, Fluvastatin, lovastatin, pravastatin, and cerivastatin. Among these forms, atorvastatin and simvastatin are more widely used than others in Thailand.

There are several studies regarding the relationship between statin and MPOD. One study stated that there was a significantly lower risk for AMD in individuals 68 years and above but not in a group of 40-67 years old individuals which may be explained by the duration of taking statin (Roizenblatt et al., 2018). Another study showed the reduction of MP value in patients taking simvastatin 20mg daily whereas no significance in patients taking simvastatin 10mg. It can be concluded that there is controversy regarding the effect of statin on MPOD.

Since the main effect of statins are to reduce the serum cholesterol level, which is one of the main factors in transporting macular pigments to the retina, the patients taking long-term statin therapy are believed to have effects on macular pigment distribution and in turn lower MPOD value. Moreover, there are only studies about the different levels of MPOD using different dosages and duration of Simvastatin but no prior study on effects of other statin drugs on MPOD value. Atorvastatin is the second most used drug for hypercholesterolemia after simvastatin. Therefore, this study intends to analyze the effects of Atorvastatin on MPOD value.

1.2 Research Question

Is there any difference between MPOD value of patients using Atorvastatin 10mg for more than 6 months and normal people?

1.3 Research Objective

To study the effect of Atorvastatin on the level of Macular Pigment Optical Density in people taking Atorvastatin 10mg for more than 6 months.

1.4 Research Hypothesis

H1: Patient taking Atorvastatin shows reduced MPOD value.

1.5 Conceptual Framework

Carotenoids, Lutein, and Zeaxanthin are bound to LDL Cholesterol and HDL Cholesterol which distributes them to the retina as macula pigments. Atorvastatin as an HMG-CoA reductase inhibitor lowers serum cholesterol which decreases the distribution of macula pigments and then achieving in the decline of macula pigment optical density (MPOD).

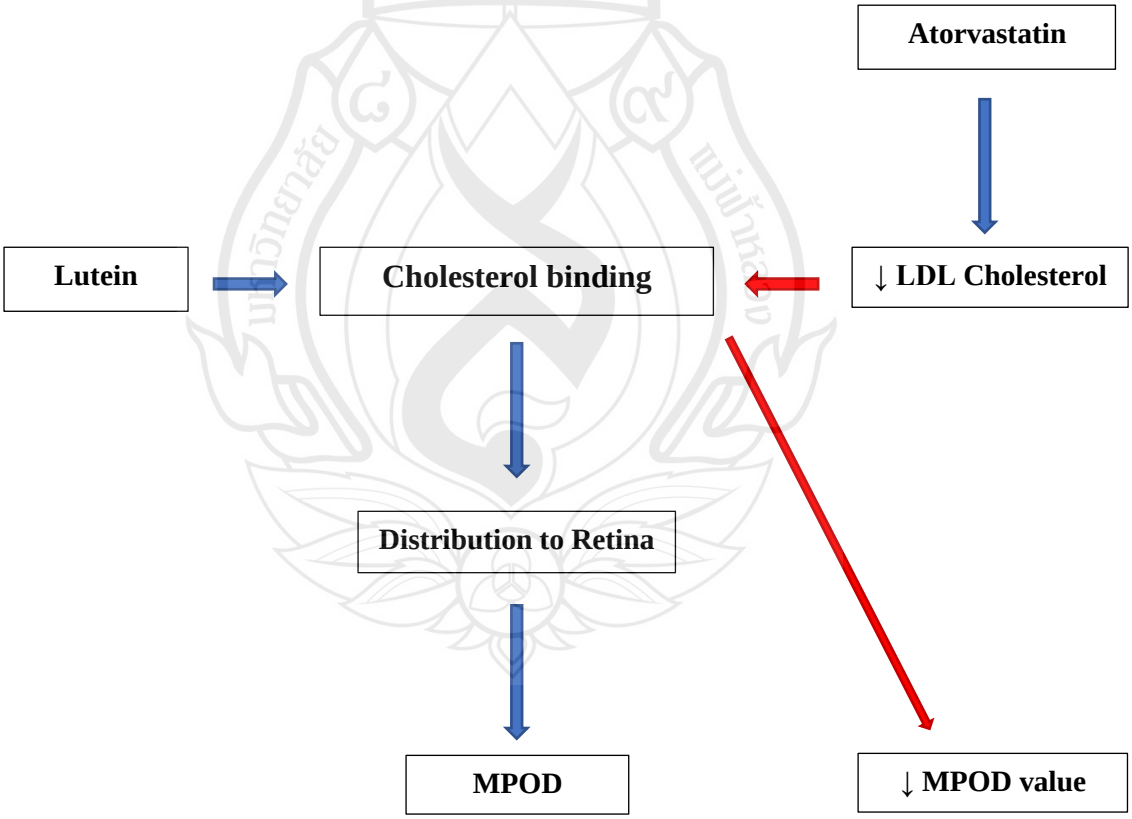

Figure 1.1 Conceptual framework of study

1.6 Definition of Technical Terms

1.6.1 Hypercholesterolemia: is defined as the high plasma cholesterol levels, especially increase in low-density lipoprotein (LDL) with or without normal plasma triglycerides

1.6.2 Macular Pigment Optical Density, MPOD: is an estimation of the blue light attenuation of macular pigment and is directly proportionate to the amount of lutein and zeaxanthin (concentration x pathlength x area) integrated over the region of macular pigment deposition in the macula. The normal level of optical density (usually refer as density units) varies between 0 and 1, in the center of the macula. According to the Macula Pigment Consensus Panel, the central MPOD is more than 0.5 d.u. (density units) is considered high, between 0.2 to 0.5 d.u. is mid-range and below 0.2 d.u. is considered to be low range.

1.6.3 HMG CoA Reductase Inhibitor: also known as Statin are HMG-CoA (3-hydroxy-3-methylglutaryl-coenzyme A) reductase (HMGR) inhibitor which effectively lowers serum cholesterol and reduces illness and mortality in those who are at high risk of cardiovascular disease.

1.6.4 LDL Cholesterol: known as low-density lipoprotein cholesterol is one of the five major groups of lipoprotein which circulates in the blood and transports all the fat molecules around the body.

1.6.5 Lipid profile is a panel of blood tests to estimate abnormalities in serum lipid level. The lab usually consists of total cholesterol level, low-density lipoprotein cholesterol (LDL-C), high-density cholesterol (HDL-C), and triglycerides level.

1.6.6 Lutein and Zeaxanthin: are naturally occurring carotenoids that can be found abundantly in plants. Lutein and Zeaxanthin are isomers and both can be interconverted into meso-zeaxanthin in the body.

CHAPTER 2

LITERATURE REVIEW

2.1 Hypercholesterolemia

2.1.1 Definition of Hypercholesterolemia

Hypercholesterolemia is defined as high plasma cholesterol levels, especially an increase in low-density lipoprotein (LDL) without or without normal plasma triglycerides. The limits to define hypercholesterolemia can be established according to the plasma level of total and LDL cholesterol above the 95th percentile corrective for age and gender in each population (Huhtaniemi, 2018). “The definition of dyslipidemia in Thailand's National Health Examination Survey (NHES) conducted in 2009 was based on the Third Adult Treatment panels (ATP III) which mean that people with different cardiovascular risk levels have different cut-off blood LDL cholesterol level.” (National Cholesterol Education Program [NCEP], 2002).

2.1.2 Prevalence of Hypercholesterolemia

Hypercholesterolemia is a major risk factor for stroke and cardiovascular accidents as well as associated with the prevalence of type II Diabetes Mellitus. Epidemiological evidence shows the strong association between raised cholesterol and vascular deaths (Collaboration, 2007). According to World Health Organization (WHO) Global Health Observatory Data collected in 2008, the global prevalence of increased total cholesterol (≥ 5.0 mmol/l) was 39%; males at 37% and females at 40% respectively.

2.1.3 Classification of Hypercholesterolemia

Hypercholesterolemia can be classified into 2 categories:

2.1.3.1 Primary or Familial Hypercholesterolemia: usually due to the mutation in LDL-receptor gene (LDLR) that is required to encode LDL receptor protein

to remove LDL from circulation or apolipoprotein B (ApoB) which is required in binding with the receptor.

2.1.3.2 Secondary or Acquired Hypercholesterolemia: the most common causes include Diabetes Mellitus, as a side effect from the use of certain drugs such as thiazide diuretics, beta-blockers, estrogens, and postprandial hyperlipidemia that is a normal increase following ingestion of food.

2.1.4 Diagnosis of Hypercholesterolemia

Hypercholesterolemia diagnosis is mainly based on fasting blood cholesterol levels. As National Cholesterol Education Program (NCEP) stated in Adult Treatment Panel III (ATP III), the LDL-C level of <100mg/dl should be called optimal level. The serum LDL-C level of 160-189 mg/dl is considered high and >190mg/dl is regarded as very high or severe hypercholesterolemia (Sniderman, Tsimikas & Fazio, 2014).

Table 2.1 ATP III classification of LDL, total cholesterol

LDL Cholesterol (mg/dl)	
<100	Optimal
100-129	Near optimal/above optimal
130-159	Borderline High
160-189	High
≥190	Very High
Total Cholesterol (mg/dl)	
<200	Desirable
200-239	Borderline High
240	High
HDL Cholesterol (mg/dl)	
<40	Low
>60	High

Source Norman and Robert (2001)

2.1.5 Complications of Hypercholesterolemia

High cholesterol can cause a dangerous accumulation of cholesterol and other deposits on arterial walls causing atherosclerosis which reduces the blood flow and leads to serious complications such as carotid artery disease, coronary artery disease including angina and heart attack, peripheral artery disease, and stroke. Studies are proving that the serum cholesterol level plays a crucial role in mortality due to cardiovascular disease. It is also claimed that patients with low dietary intake of fat and low serum cholesterol level promote lower mortality from coronary heart disease and lower risk for certain cancers (Juha, Aulikki, Sven & Martti, 1992).

2.1.6 Treatment

According to the expert panel based on the data various analyses, the clinical practice recommends the control of blood cholesterol levels to reduce Atherosclerotic cardiovascular disease (ASCVD) risk which includes coronary heart disease (CHD), stroke, and peripheral arterial disease from atherosclerotic origin.

Lifestyle counseling should be considered a foundation for statin therapy from initial to follow-up visits to improve the overall risk factor profile due to hypercholesterolemia. A healthy diet or lifestyle modifications were recommended as background treatment for the cholesterol-lowering drug therapy (Robert et al., 2014). Treatment for related risk factors such as hypertension and lifestyle changes especially avoidance of smoking should be adapted.

In the trials reviewed, the crucial factor in reducing ASCVD events is the timely initiation of moderate-intensity therapy which is targeted to lower LDL cholesterol by approximately 30% to <50%, or high-intensity statin therapy which will lower LDL cholesterol by ≥50%. The Cholesterol Treatment Trialists (CTT) conducted in 2010 calculated the percentage of reduction in LDL cholesterol for a specific type of statin and dose in individual meta-analysis.

Table 2.2 High, moderate, and low-intensity statin therapy (used in the RCTs reviewed by the expert panel)*

High-Intensity Statin Therapy	Moderate Intensity Statin Therapy	Low-Intensity Statin Therapy
On average, lowers LDL-C by approximately ≥50%	On average, lowers LDL-C by approximately 30% to <50%	On average, lowers LDL-C by <30%
Atorvastatin (40)80mg	Atorvastatin 10(20) mg	Simvastatin 10mg
Rosuvastatin 20(40) mg	Rosuvastatin (5) 10 mg	Pravastatin 10-20 mg
	Simvastatin 20-40 mg	Lovastatin 20 mg
	Pravastatin 40 (80) mg	Fluvastatin 20-40 mg
	Lovastatin 40 mg	Pitavastatin 1 mg
	Fluvastatin XL 80 mg	
	Fluvastatin 40 mg BID	
	Pitavastatin 2-4 mg	

Source Neil et al. (2014)

2.2 HMG CoA Reductase Inhibitor (Statin)

HMG CoA Reductase Inhibitor or most known as stains are a class of lipid-lowering drugs especially LDL cholesterol which is highly related to the illness and mortality due to cardiovascular diseases. The studies proved that statins if given in standard dose can lower LDL-C by 18% to 55%, which also depends on the type of statin in use. The medical usage of statins can be divided into primary prevention, which prevents the risk of heart disease in high cholesterol, and secondary prevention, which decreases the rate of mortality in people with preexisting cardiovascular disease.

Generally, statins are classified into two groups: the synthetic group which includes Atorvastatin, Cerivastatin, Fluvastatin, Pitavastatin, Rosuvastatin, and naturally occurring fermentation-derived groups such as Lovastatin, Mevastatin, Pravastatin.

2.2.1 Mechanism of Action

Statins being similar to 3-hydroxy-3-methylglutaryl-CoA (HMG CoA) on a molecular level, competitively inhibits the HMG CoA reductase enzyme which is the rate-limiting enzyme in the mevalonate pathway as seen in Figure 2.1. This competition reduces the rate of HMG-CoA reductase to produce mevalonate, which is the important molecule in the cascade that produces cholesterol. Statins block the cholesterol synthesis pathway in the liver by inhibiting HMG-CoA reductase. This is significant in controlling blood cholesterol levels because most circulating cholesterol in the blood comes from internal manufacturing rather than the external source or diet. As the liver production of cholesterol reduces, serum cholesterol levels will also decrease. Statins also act by increasing LDL uptake into the liver where the cholesterol will be reprocessed into bile salts and other byproducts, reducing the amount of circulating cholesterol in the blood. Moreover, researches are proving the pleiotropic effect of statins such as decreasing oxidation of LDL cholesterol, positive effects on endothelial function and blood flow, promoting the stability of atherosclerotic plaques, reducing vascular inflammation, and inhibiting proliferation of vascular smooth muscle proliferation and platelet aggregation. (James & Ulrich, 2005).

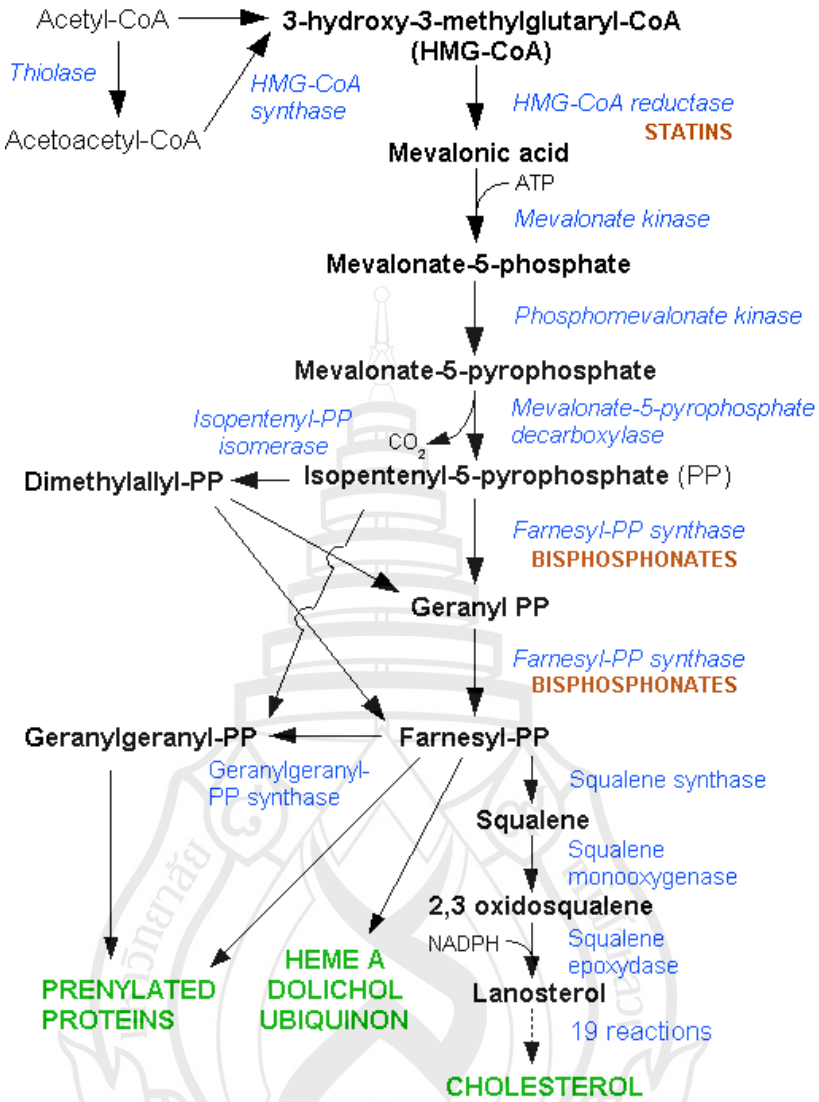

Figure 2.1 HMG CoA reductase inhibitor pathway

2.2.2 Atorvastatin

Atorvastatin is one of the most commonly used medications for dyslipidemia in the world. It is a completely synthetic compound, unlike most other statins. The primary site of action of Atorvastatin is the liver where the majority of both cholesterol synthesis and LDL clearance takes place. Atorvastatin can effectively lower total cholesterol by 27% to 37.9%, LDL cholesterol by 37.1% to 51.7%, and triglycerides by 18% to 28.3% when used within the recommended dosage range of 10-80 mg/day. The extent of LDL reduction correlates to the dosage of atorvastatin in use (Adams, Tsang & Wright, 2015).

Atorvastatin is proved to have more efficacy and potent in lowering LDL cholesterol than simvastatin which is commonly used in some countries (Farnier, Portal & Maigret, 2000).

2.3 Association of LDL Cholesterol and Transport of Lutein and Zeaxanthin

Circulating lipoproteins can be classified into six groups: very-low-density lipoproteins (VLDL), intermediate-density lipoproteins (IDL), low-density lipoproteins (LDL), high-density lipoproteins (HDL), chylomicrons, and chylomicron remnants. Lipoproteins are usually associated with high-affinity receptors on the cell surface to be transported in the body and regulate lipid metabolism. (Mahley, Innerarity, Rall & Weisgraber, 1984)

Lipoproteins are responsible for the transport of plasma carotenoids in the body. 55% of total carotenoids are transported on LDL, whereas 33% is associated with HDL and only 10-19% with VLDL (Beverly & John, 1993). This finding suggests that macular pigment may be influenced by the delivery and distribution of the carotenoids to the retina by an individual's lipoprotein and lipoprotein profile in the blood. (Sylvie & John Chapman, 1997).

2.4 Macula Pigment

Macular pigment (MP) is known to protect the oxidative damage to the retina by absorbing blue-light which is a short wavelength and usually harmful to the eye (Beatty et al., 1999). Macula pigment is mainly located in the fibers of Henle in the fovea site which contains the axons of the foveal cone and in the inner part of the nuclear layer at the parafoveal site. (Snodderly, Auran & Delori, 1984; Trieschmann et al., 2008). The dietary hydroxy carotenoids, lutein, and zeaxanthin are the main components of MP (Landrum, Bone & Kilburn, 1996). The concentration of carotenoid in the blood and concentration of macular carotenoid in the retina forming MP is significantly different. The macular carotenoids are responsible for painting yellow color to macula lutea and provide excellent antioxidant properties for the retina (Beatty et al., 1999; Landrum et al.,

1996). The other carotenoid named meso-zeaxanthin which is the stereoisomer of zeaxanthin, cannot be found in diet or detected in serum is also present in a large amount within macula (Bone et al., 1997). Lutein and zeaxanthin are not synthesized in the body and are solely acquired from a dietary source such as dark green vegetables and various orange or yellow fruits and vegetables and egg yolks (Chug-Ahuja et al., 1993; Handelman, Nightingale, Lichtenstein, Schaefer & Blumberg, 1999).

Macula pigment absorbs the short wavelength of visible light at 460nm maximally (Snodderly et al., 1984): the shorter wavelength, blue waves are potent and competent to produce reactive oxygen species (ROS) from endogenous photosensitizers like lipofuscin and are more harmful than longer wavelengths. Moreover, lutein and zeaxanthin provide an optical filter of antioxidant protection to the human retina from exposure to high-energy blue light and inhibit the photo-oxidation and peroxidation of long-chain polyunsaturated fatty acids. (De La Paz & Anderson, 1992).

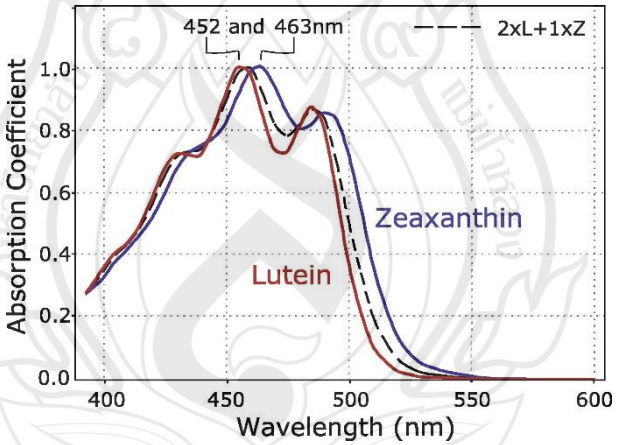

Figure 2.2 Absorption spectrum of Lutein (red), zeaxanthin (blue), and combined lutein and zeaxanthin (black dotted line) in olive oil. The latter showing close approximate to the absorption of macular pigment in the human eye

2.4.1 Macula Pigment Optical Density (MPOD)

Macular pigment optical density or MPOD is a measurement of the amount of blue light attenuation by the macular pigment in the retina and it is directly related to the amount of the integrated macular carotenoids; lutein and zeaxanthin over the region of

macula pigment deposition. MPOD is usually described in optical density level or density units (d.u) and the normal range in the center of the macula is from 0 to 1. (Bone et al., 1992).

2.4.2 Factors contributing to MPOD

As one of the relevant factors in the development of some retinal diseases is oxidative stress (Burstedt, Ristoff, Larsson & Wachtmeister, 2009; Ding, Patel & Chan, 2009), the protective role of macula pigment in some ocular diseases such as age-related macular degeneration, has been well studied. (Beatty et al., 1999; San Giovanni et al., 2007). Several pieces of research have provided the influence of social factors such as age, sex, body mass index (BMI), eye color, and other environmental factors on the Macular Pigment Optical Density (MPOD) value. The study described that females tend to have higher MPOD value than males of the same age group (Curran Celentano, Burke & Hammond Jr, 2002; Hammond, Ciulla & Snodderly, 2002) whereas old age, particularly 60 years and above is proved to have lower MPOD value than younger age population (Curran Celentano et al., 2002). There is a lower value in people with higher BMI (Curran Celentano et al., 2002; Hammond et al., 2002). Due to the lesser amount of melanin density present, the lighter Iris color has a lower MPOD value (Curran Celentano et al., 2002; Wolf-Schnurrbusch et al., 2007). There is one experimental study proving that supplementation with oral carotenoids can provide protection and reduce oxidative damage of the retina. (Kowluru, Menon & Gierhart, 2008).

2.4.3 MPOD Values

As central MPOD value ranges from undetectable to 1 density units (d.u.) at the maximum and is relatively proportionate to the amount of xanthophyll pigment, the Macula Pigment Consensus Panel stated that it is more important to identify the individuals at risk for age-related eye disease through the level of central MPOD value. The central MPOD value of above 0.5 d.u is considered high range, 0.5 d.u to 0.2 d.u is mid-range and the value below 0.2 d.u is considered low. Data collected from the previous studies done in the U.S population (n=846) showed approximately 43% has central MPOD below 0.2 d.u and 16% of the population have a value below 0.1 d.u. The result is also consistent with the study done in healthy Irish subjects (n=828). Collected under a similar age group and conditions, the mean central MPOD in this study was 0.30

d.u. which is corresponding to the result of the other study of central MPOD value between 0.21 to 0.44 d.u. The panel suggested that it is still controversial whether central MPOD declines with age or not. These variations in results may be accountable to population selection such as clinic-based study versus recruited population than the difference in research methodology since a variety of technologies has been used to study this relationship of age and MPOD. The panel also highlighted that mass screening of MPOD in the general population should be considered for a better understanding of potential age-related MPOD changes. (Bernstein, Delori, Richer, van Kuijk & Wenzel, 2010).

2.5 Macular Pigment Screener II (MPS II)

Macular Pigment Screener II (MPS II), also known as MPS9000 is one of the recently introduced devices to measure the Macular Pigment Optical Density (MPOD) for screening and detection of ophthalmic diseases such as age-related macular degeneration (Makridaki, Carden & Murray, 2009).

2.5.1 Advantages of using MPS II

The main benefit of using the MPS II screener is that the device is relatively inexpensive and it is not necessary for pupillary dilation since it uses the heterochromatic flicker photometry technology (Van Der Veen et al., 2012). Moreover, the studies had proven the validity and repeatability of MPOD measurement using this device (Bartlett, Howells & Eperjesi, 2010; Howells, Eperjesi & Bartlett, 2011; Leung, 2008). The footprint is compact and portable with regular improvements and software updates including unparalleled data access. It is also designed to be user-friendly with easy-to-follow manuals for both patient and the operator. Patient data storage is also embedded for continuous monitoring of MPOD values. Moreover, the operator can monitor if the test is being performed correctly or not from how the curve appears during the procedure (Van Der Veen et al., 2012). Although the device is programmed to control the light intensity and the sequence of the test, people with low visual acuity and young children may have difficulty identifying the flicker sensitivity and may not be suitable for the test (Bartlett et al., 2010; Howells et al., 2011; Leung, 2008).

2.5.2 Technology of MPS II

Heterochromatic Flicker Photometry (HFP) technology is mainly based on the macula pigment absorption spectrum at the macula and fovea of the retina. (Bartlett et al., 2010; Howells et al., 2011; Leung, 2008). This MPS II device polishes the HFP technology to be more accessible and uses it to measure the MPOD. (Van Der Veen et al., 2012). HFP measures the MPOD by using two light stimuli with an alternating wavelength which is seen as the flicker to the subject. Macula pigment at the fovea and parafoveal area have will have maximum absorption for the shorter wavelength blue light and will absorb minimally for a green/yellow light with a longer wavelength (Bartlett et al., 2010; Howells et al., 2011). The alternating amount of green and blue light will be emitted until the subject can respond to minimal flicker (Howells et al., 2011; Leung, 2008).

In the initial part of the test, the fovea region will be targeted with the flickering light where there is a higher density of carotenoids and measurement will take a longer duration (Bartlett et al., 2010; Howells et al., 2011). After that, the same process will be repeated at the parafoveal area where there are minimal carotenoids and therefore the time taken is believed to be relatively shorter (Bartlett et al., 2010; Howells et al., 2011; Leung, 2008). MPOD is calculated by the log ratio of the two values at the fovea and parafovea (Howells et al., 2011). Since the conventional HFP technique requires the observer to respond to a minimal flicker setting, the users often face problems of adaptation difficulties. MPS uses the same principle but is modified to lessen the difficulty by decreasing the frequency of blue-green alternation as the subject responds to the flicker.

In contrast to the traditional method where the ratio of blue-green light is determined by the user response to the intensity of the flicker, this technique needs the observer to press the buttons as the flicker appears automatically at different light ratios. The adaptation is more user-friendly in that it can be used for screening of mass population with adequate accuracy rate for the patients to have a clear cut-off point and consider to get advise on their lifestyle, diet, and ocular diseases from the clinician.

The pre-test routine is done to determine the different flicker sensitivity of each individual to provide the luminance contrast of the lights to be set up (Makridaki, Carden & Murray, 2009). In the main test, the blue-green ratio is set initially and the frequency of blue light (at 460 nm) and green light (540 nm) slowly and automatically decrease from

55Hz. The observer views the central target through the eyepiece and gives a response to the flicker by pressing a button. Then the flicker rate is reduced from the initial frequency of 55Hz with the altered blue-green ratio until the observer detects a flicker. The sequence of obtaining a flicker threshold is continued until a curve showing the minimum point where blue target luminance for central viewing is obtained as shown in Figure 2.3. The process of flicker detection for blue-green ratios is repeated until a new minimum point for peripheral viewing is obtained. The MPOD measurement is determined by the difference between the two minima. Approximately two to three minutes of total testing time is required for one eye.

Figure 2.3 The MPS II screener device

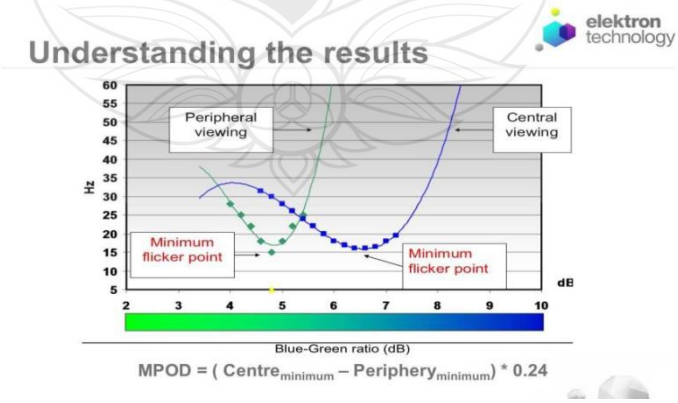

Figure 2.4 The minimum flicker point of blue light versus green-yellow light

2.5.3 MPS II target

The target is the most important part of the MPS II screener. The instrument should be kept clean and free from dust especially the lens and optics. The side of the eye not being tested should be covered. Both sides of the eye should be examined for central and peripheral tests.

2.5.4 How to Measure MPOD

Three circles are visible against plain white background through the view from the eyepiece as shown in Figure 2.4. Once the test begins, the smaller dot in the center will change to blue-green color and a flicker will be seen. Two larger dots on both sides act as fixation targets for the peripheral test.

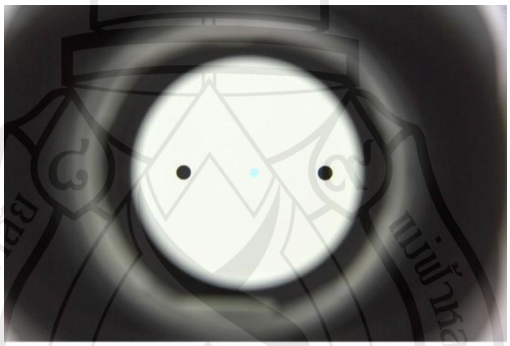

Figure 2.5 The view through the eyepiece

The machine has two test modes; the "Standard Mode" in which the patient performs only central test where MPOD is compared with age normative data and the "Detailed Mode" in which both central and peripheral test is done to get the 'absolute' MPOD value. The detailed model is done in patients who do not follow the age-normal data such as diabetic patients and related ocular conditions.

Each response to the flicker done by the patient will be recorded on the graph allowing the operator to check whether the test is performed correctly or not from the way the curve develops during the procedure. The test should be repeated if there is a poor curve or if there is a significant difference between equivalent minimum readings. The poor quality curves will be excluded from the MPOD calculation. The average test time

for the standard mode to complete is approximately 90 seconds per eye and the detailed mode takes around 2-3 minutes per eye. The final result will appear with the MPOD value of both eyes on the same print out as shown in the figure below.

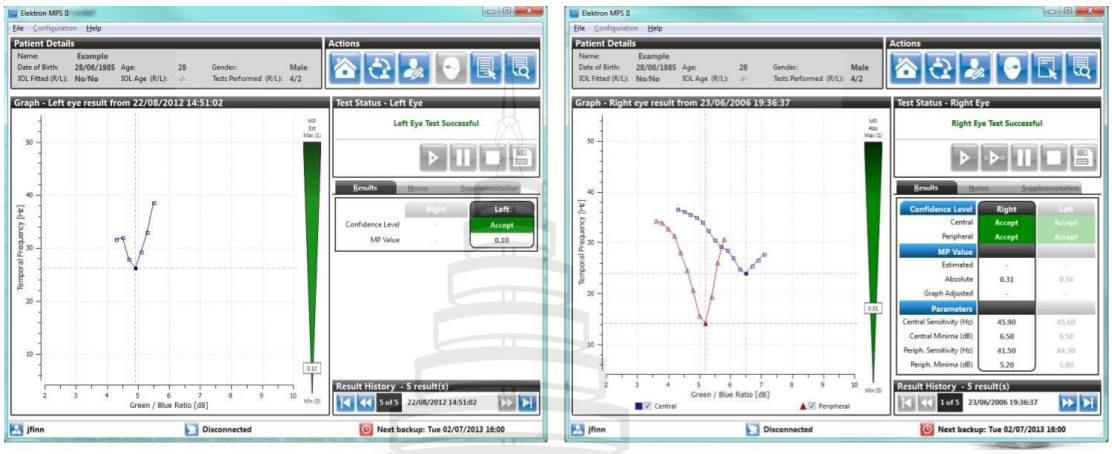

Figure 2.6 The test result of the MPOD; standard mode (L) and detailed mode (R)

CHAPTER 3

RESEARCH METHODOLOGY

3.1 Research Design

Cross-sectional Analytical study.

3.2 Study Population

3.2.1 Asian males and females within 30-60 years of age, previously diagnosed with Hypercholesterolemia by the physicians and currently taking atorvastatin 10mg for at least 6 months were randomly selected as the volunteers.

3.2.2 Asian males and females between 30-60 years of age, who are not taking atorvastatin.

3.3 Sample Size

$$n = \frac{Z^2_{\alpha/2}\sigma^2}{d^2}$$

n = Sample size

Set $\alpha = 0.05$, $Z_{\alpha/2} = 1.96$

σ = 0.12, The standard deviation of MPOD value in the previous study (Piyabhorn, 2019)

d = 0.05, The absolute error or precision

$$n = \frac{1.96^2 \times 0.12^2}{0.05^2}$$

n = 22

There will be a total of 44 volunteers divided into 2 groups, case, and control with 22 people in each. The first group or Case group, being people currently taking Atorvastatin for more than 6 months, and the second group or control group, being normal healthy people.

3.4 Sample Selection

3.4.1 Inclusion Criteria

3.4.1.1 Age between 30-60 years

3.4.1.2 Patients who are taking Atorvastatin 10mg for at least 6 months

3.4.2 Exclusion Criteria

3.4.2.1 Patients who are taking lutein and zeaxanthin supplementation

3.4.2.2 Patients who are taking vitamin A and vitamin A related supplementation

3.4.2.3 Patients with corneal scar, cataract, vitreous hemorrhage

3.4.2.4 Patients with features of age-related macular degeneration and other related diseases such as glaucoma, cataract, optic nerve atrophy, diabetic retinopathy, previous lasers or surgeries on the retina, and previous eye trauma

3.4.2.5 Patients with serum cholesterol level >190 mg/dl Diagnosed Diabetes Mellitus or fasting blood sugar >126 mg/dl at the first visit

3.4.2.6 Patients with myocardial infarction, stroke

3.4.2.7 Patients with liver dysfunction or renal impairment

3.4.2.8 Patients with autoimmune disease, hyperthyroidism, hypothyroidism, or malignant tumors

3.4.3 Withdrawal Criteria

Patients with their troubles to perform the flicker sensitivity test of the Macular Pigment Screener II (MPS II).

3.5 Measurements

Macula pigment optical density (MPOD) level by Macular Pigment Screener II (MPS II)

3.6 Research Tools

3.6.1 Macular Pigment Screener II (MPS II)

3.6.2 Questionnaire

3.6.3 Result record form

3.7 Research Procedure

3.7.1 Participants are divided into two groups: case group, who are taking Atorvastatin 10mg for more than 6 months, and control group, who are not taking Atorvastatin.

3.7.2 Participants are given the questionnaire to complete which means to rule out the exclusion criteria. Questions are built on the factors that are related to the level of MPOD such as peculiars of the subject, lifestyle, dietary habits, and environmental factors. For example, age, sex, eye color, smoking history, duration of blue-light exposure per day, vitamin and supplements, and history of diabetes and AMD are important factors in determining the MPOD level. The questionnaire is provided as an appendix.

3.7.3 All participants were explained and provided with written consent form and information sheets before the study start.

3.7.4 Before starting the measurement, all participants were explained and given instructions on how to perform the test on the MPS II screener by the investigator. Then participants took the test to measurement the MPOD by MPS II. Each participant took approximately 60-90 seconds for the test to be done.

3.7.5 Measurement results were collected and analyze the collected results.

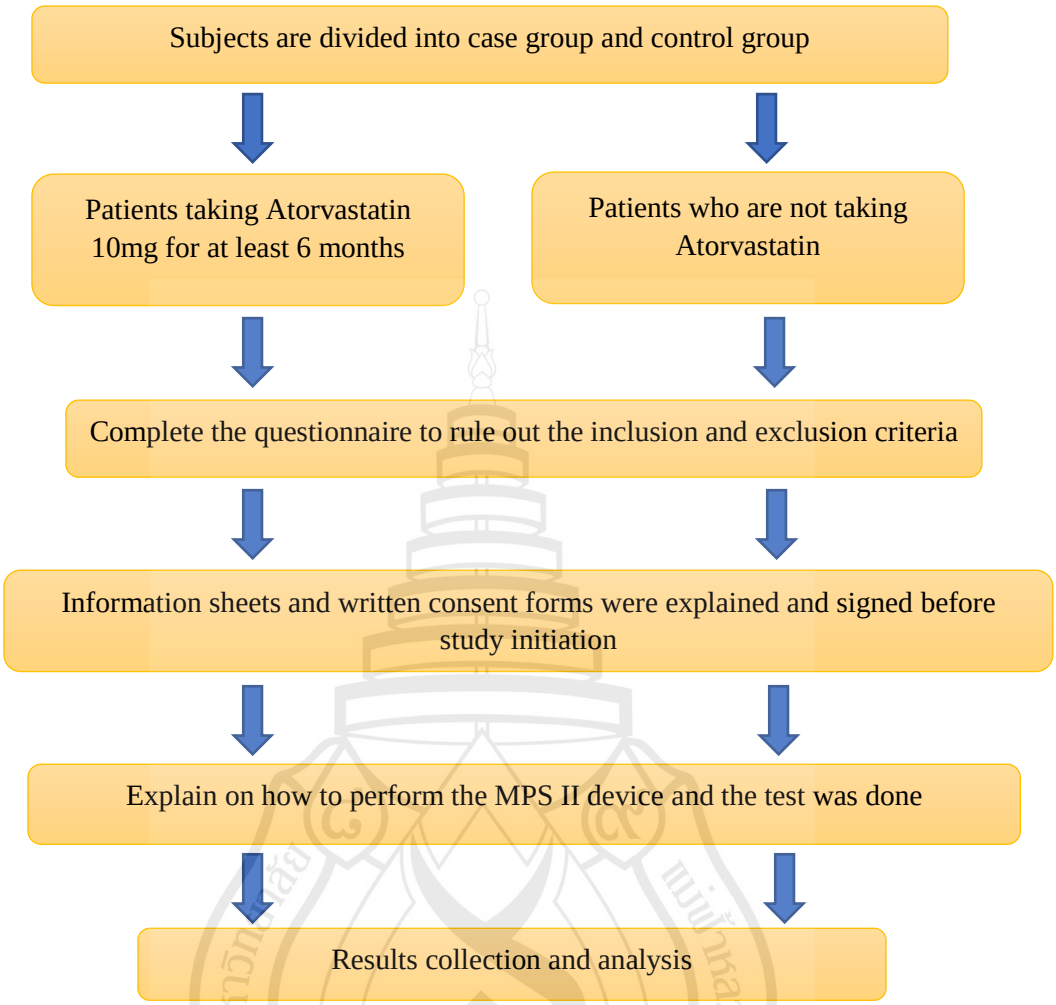

Figure 3.1 Research procedure

3.8 Ethical Consideration

This study is approved by the Mae Fah Luang University Committee on Human Research in compliance with international guidelines such as Declaration of Helsinki, the Belmont Report, CIOMS Guidelines and the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use-Good Clinical Practice (ICH-GCP). COA: 171/2020

3.8.1 Risks

MPSII device is approved by Thailand FDA and is proved to have little or no danger to the user during or after measurement.

3.8.2 Benefits

3.8.2.1 For the patients taking atorvastatin for hypercholesterolemia, there will be awareness of the risk of age-related macular degeneration (AMD) and the importance of macula pigment for continuous screening and evaluation.

3.8.2.2 For the public benefit, the measurement of macular pigment density is a simple procedure with a shorter time requirement and screening can be done with few side effects and is relatively cheap.

3.8.2.3 For the field of biomedical research, this study will help to describe the relationship between reduced MPOD value and moderate use of atorvastatin in hypercholesterolemia since there are still limited and conflicting data regarding the variations of this association.

3.8.3 Respect to person

The results of every participant are only given to them and kept confidential.

3.8.4 Justice

3.8.4.1 The patients participate voluntarily, without any payment or charges on the tests and instruments.

3.8.4.2 All volunteers have an equal chance to test MPOD level.

3.9 Statistical Analysis

3.9.1 Descriptive Statistics:

The demographic characteristics of all subjects were reported with

3.9.1.1 Qualitative data - frequency and percentage (%) for categorical variables

3.9.1.2 Quantitative data - mean and standard deviation for continuous variables.

3.9.2 Inferential Statistics:

Kolmogorov-Smirnov test – To test whether the sample belongs to normal distribution.

T-test or U test – To compare the MPOD value between patients taking Atorvastatin 10mg for 6 months and normal subjects.

CHAPTER 4

RESULTS

4.1 General Characteristic of the Sample

General demographic data of 44 participants were divided into currently taking atorvastatin 10 mg for at least 6 months group (Study group) and did not take atorvastatin (Control group). Data were recorded and analyzed with descriptive statistics in the following table 4.1.

Table 4.1 Participants' demographic characteristics

Demographic	Study group (n=22)	Control group (n=22)
Sex		
Male	12	9
Female	10	13
Age (years)		
Mean±SD	44.00±9.84	36.64±6.49
Min - Max	30-60	30-54
Smoking, n(%)		
Yes	8	3
No	14	19
Alcohol Drinking, n (%)		
Yes	8	3
No	14	19

Table 4.1 (continued)

Demographic	Study group (n=22)	Control group (n=22)
Physical activity, n (%)		
Yes	8	11
No	14	11
Drug allergy, n (%)		
Yes	1	0
No	21	22
Skin sensitivity		
Yes	2	0
No	20	22
Strong sunlight exposure		
Yes	0	0
No	22	22
Sunglass usage		
Yes	1	0
No	21	22
Screen usage (hours/day)		
Mean±SD	7.18±2.11	8.36±1.33
Min - Max	4-10	6-10
Eye color, n(%)		
Black	12	13
Brown	10	9

According to table 4.1 that demonstrated the demographic data of the participants in the study group, most of the subjects were 12 male (54.5%) and 10 female (45.5%). The mean age of the subject was 44.00±9.84 years. There were 8 subjects (36.4%) who had smoking, 8 subjects (36.4%) drinking alcohol, 8 subjects (36.4%) engaged in physical activity, and 1 subject (4.5%) drug allergy. Furthermore, two subjects (9.1%)

had skin sensitivity, no subject got exposed to strong sunlight and 1 subject (4.5%) regularly wear sunglasses. The mean screen usage time was 7.18±2.11 hours/day. The majority of the subjects had eye color was black 12 subjects (54.5%) and brown 10 subjects (45.5%), respectively.

For participants in the control group, most of the subjects were 13 female (59.1%) and 9 male (40.9%). The mean age of the subject was 36.64±6.49 years. There were 3 subjects (13.6%) who had smoking, 3 subjects (13.6%) drinking alcohol, 11 subjects (50.0%) engaged in physical activity, and no subject with drug allergy. Furthermore, no subjects had skin sensitivity, got exposed to strong sunlight, and regularly wear sunglasses. The mean screen usage time was 8.36±1.33 hours/day. The majority of the subjects had eye color was black 13 subjects (59.1%) and brown 9 subjects (40.9%), respectively.

Table 4.2 Underlying disease and treatments apart from hyperlipidemia

Demographic	Study group	Control group
Underlying disease, n (%)		
Hypertension	8 (36.4%)	1 (4.5%)
Diabetes mellitus	8 (36.4%)	7 (31.8%)
Heart disease	4 (18.2%)	0 (0.0%)
Metabolic syndrome	0 (0.0%)	0 (0.0%)
Gout	3 (13.6%)	0 (0.0%)
Osteoarthritis	1 (4.5%)	0 (0.0%)
Dementia/Alzheimer	0 (0.0%)	0 (0.0%)
Migraine	0 (0.0%)	0 (0.0%)
Glaucoma	0 (0.0%)	0 (0.0%)
Cataract	1 (4.5%)	0 (0.0%)
Eye trauma	0 (0.0%)	0 (0.0%)
AMD	0 (0.0%)	0 (0.0%)
Diabetic Retinopathy	0 (0.0%)	0 (0.0%)
Diabetic Macula Oedema	0 (0.0%)	0 (0.0%)

Table 4.2 (continued)

Demographic	Study group	Control group
Operation/treatment to the eye, n (%)	0 (0.0%)	0 (0.0%)
Other major operation, n (%)	3 (13.6%)	0 (0.0%)
Other minor operation, n (%)	3 (13.6%)	0 (0.0%)

According to table 4.2 that demonstrated the underlying disease and treatments of the participants in the study group, it was found that 8 subjects (36.4%) with hypertension, 8 subjects (36.4%) with diabetes mellitus, 4 subjects (18.2%) with heart disease, 3 subjects (13.6%) with gout, 1 subject (4.5%) with osteoarthritis and 1 subject (4.5%) with cataract, respectively. The history of operation it was found that 3 subjects (13.6%) got other major operation, 3 subjects (13.6%) got other minor operation and no subject got operation/treatment to the eye.

For participants in the control group, were 7 subjects (31.8%) with diabetes mellitus and 1 subject (4.5%) with hypertension, respectively. The history of operation it was found that no subject got operation/treatment to the eye, other major and minor operation.

Table 4.3 Supplements and medicines

Demographic	Study group (n=22)	Control group (n=22)
Fruits & veggies	16	16
Eggs	14	16
Oily fish intake	12	17
Lutein & Zeaxanthin	0	0
Multivitamin	1	7
Vitamin B	0	2
Vitamin C	12	14
Vitamin D	8	7
Vitamin E	0	0

Table 4.3 (continued)

Demographic	Study group (n=22)	Control group (n=22)
Astaxanthin	6	2
Bilberry	0	0
Omega 3 fish oil	13	8
Lecithin	0	0
CoQ10	5	3
Grape seed extract	0	0
Pine Bark extract	0	0
Rosehips	0	0
Other supplements	1	0
Chloroquine / Hydroxychloroquine / Ethambuol / Tamoxifen	0	0
Duration of taking Atorvastatin 10mg/day		
< 12 months	11	-
≥ 12 months	11	-

According to table 4.3 that demonstrated the supplements and medicines data of the participants in the study group, it was found that 16 subjects (72.7%) eat fruits & veggies, 14 subjects (63.6%) eat eggs and 12 subjects (54.5%) eat oily fish, respectively. For supplements intake it was found that 13 subjects (59.1%) take Omega 3 fish oil, 12 subjects (54.5%) take Vitamin C, 8 subjects (36.4%) take Vitamin D, 6 subjects (27.3%) take Astaxanthin, 5 subjects (22.7%) take CoQ10, 1 subject (4.5%) take Multivitamin and 1 subject (4.5%) take other supplements, respectively. For the duration of taking Atorvastatin, it was found that 11 subjects (50.0%) take less than 12 months and 11 subjects (50.0%) take more than or equal 12 months. Furthermore, it was found that all participants in the study group did not take Chloroquine / Hydroxychloroquine / Ethambuol / Tamoxifen.

For participants in the control group, it was found that 17 subjects (77.3%) eat oily fish, 16 subjects (72.7%) eat fruits & veggies and 16 subjects (72.7%) eat eggs, respectively. For supplements intake it was found that 14 subjects (63.6%) take Vitamin C, 8 subjects (36.4%) take Omega 3 fish oil, 7 subjects (31.8%) take Multivitamin, 7 subjects (27.3%) take Vitamin D, 3 subjects (13.6%) take CoQ10, 2 subjects (9.1%) take Vitamin B and 2 subjects (9.1%) take Astaxanthin, respectively. Furthermore, it was found that all participants in the control group did not take Chloroquine / Hydroxychloroquine / Ethambuol / Tamoxifen.

4.2 Macula Pigment Optical Density (MPOD)

The objective of this study was to examine the compare MPOD of participants who are taking atorvastatin 10 mg for at least 6 months in currently (Study group) and who did not take atorvastatin (Control group). The results of this study were shown as follows.

Table 4.4 MPOD level

MPOD	**Study group (n=22)** **Min-Max (0.05-0.58)**	**Control group (n=22)** **Min-Max (0.24-0.86)**
0.00 – 0.25 du.	6	1
0.26 – 0.30 du.	3	1
0.31 – 0.40 du.	7	8
0.41 – 0.50 du.	4	4
> 0.50 du.	2	8

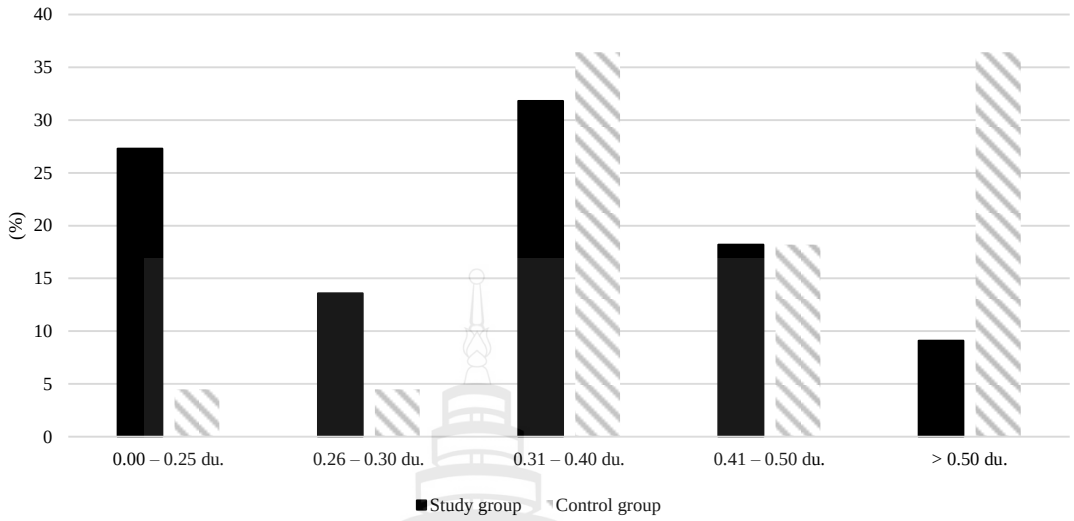

Figure 4.1 Bar graph showing co MPOD level in study group and control group

According to table 4.4 and figure 4.1 that demonstrated the MPOD level of the participants in the study group, it was found most that in 0.31 – 0.40 du. of 7 subjects (31.8%), followed by 0.00 – 0.25 du. of 6 subjects (27.3%), 0.41 – 0.50 du. of 4 subjects (18.2%), 0.26 – 0.30 du. of 3 subjects (13.6%) and more than 0.50 du. of 2 subjects (27.3%), respectively. For participants in the control group, it was found most that were 0.31 – 0.40 du. & more than 0.50 du. of each 8 subjects (36.4%), followed by 0.41 – 0.50 du. of 4 subjects (18.2%) and less than or equal 0.30 du. of 2 subjects (9.0%), respectively.

Table 4.5 Statistical analysis of MPOD between study group and control group

Group	n	Mean	Std. Deviation	Min - Max	t	df	P-value
Study group	22	0.32	0.13	0.05-0.58	-3.285	42	0.002
Control group	22	0.46	0.14	0.24-0.86			

Note P-value determine by independent t-test

* Statistically significant at the 0.05 level

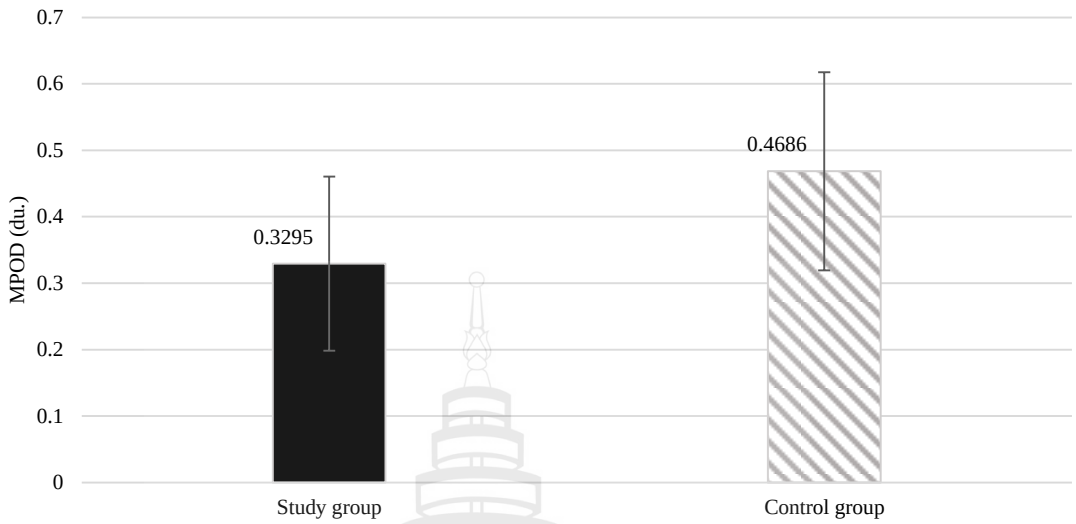

Figure 4.2 Bar graph showing the comparison of MPOD between study group and control group

According to the statistical analysis results from table 4.5 and figure 4.2, the mean of MPOD in the study group was 0.32±0.13 du. (Min-Max 0.05-0.58). For the control group, the results was 0.46±0.14 du. (Min-Max 0.24-0.86). In the comparison of MPOD between the study group and control group; it was found that mean of MPOD of the study group was significantly lower than the control group (p=0.002).

CHAPTER 5

DISCUSSION AND CONCLUSIONS

5.1 Discussion

This study is designed to study the level of Macular Pigment Optical Density in people taking Atorvastatin 10mg for at least 6 months. This research is a cross-sectional analytical study done in Asian males and females within 30-60 years of age using Macular Pigment Screener II (MPS II). The results show that the mean MPOD value in normal subjects (control group) was 0.46±0.14 du. (Min-Max 0.24-0.86) which is greater than the mean MPOD of the patients taking Atorvastatin 10mg 0.32±0.13 du. (Min-Max 0.05- 0.58) for at least 6 months (study group). The statistical analysis shows that there is a significant reduction of MPOD level in patients taking Atorvastatin 10mg for at least 6 months ($p=0.002$).

The result is consistent with the study showing there is a significantly lower level of MPOD in patients using statin more than 1 year than non-statin users. Moreover the study states that the patients using atorvastatin had lower MPOD value than simvastatin users, suggesting that type of statin and duration of receiving it also plays a significant role in MPOD value. Which may explain the fact that in the previous study done in patients receiving simvastatin, the results showed no significant difference in MPOD in patients taking simvastatin 10mg for 6-12 months and normal patients.

The serum lipoproteins; especially LDL is one of the main components in the transport of carotenoids to the retina as macular pigments. Atorvastatin, as a lipid-lowering agent which can reduce LDL by 37.1% to 51.7% in the blood, decreases the distribution of macular pigments and causes reduced MPOD value. The comparative research between Atorvastatin and Simvastatin showed that Atorvastatin is more potent and effective than the latter (Farnier et al., 2000).

As proved by previous research, MPOD level is influenced by several physical and environmental factors such as age, sex, body mass index, eye color, diet, physical activity, and amount of screen time or exposure to blue light (Curran Celentano et al., 2002). Macular pigment density also showed correlations with lutein and zeaxanthin in relation to serum lipid levels (Olmedilla-Alonso, Beltrán-de-Miguel, Estévez-Santiago & Cuadrado-Vives, 2014). In this study, there is an uneven distribution of age, sex, body mass index, physical activity, and amount of screen time between the study group and control group, which might contribute to the result of mean MPOD level.

5.2 Conclusion

In conclusion, mean MPOD in patients using Atorvastatin 10mg for at least 6 months 0.32±0.13du is significantly lower than the control group 0.46±0.14 du. The duration of patients in this study taking Atorvastatin 10mg varies from 6 months to 20 years. It will be beneficial to have an awareness of the risk associated with long term statin use and include MPOD measurement as screening test to reduce the development of serious complications such as AMD.

5.3 Limitation

The limitation of this study is that this is only a cross-sectional study and the participants involved are residents in Bangkok, who are more likely to have more screen usage with less physical activity, especially during the covid-19 pandemic

5.4 Suggestion

5.4.1 Studying the effect of statins on MPOD value will need further studies like using a different class of statins, comparison between duration and dosage of statin used.

5.4.2 Furthermore, a more refined investigation should be done on the relation between MPOD and other factors such as age, sex, BMI, and level of cholesterol in the blood.

5.4.3 A controlled, prospective clinical trial with exact dietary and/or lifestyle modifications, supplemental trials and serial measurement of serum lutein and zeaxanthin, and correlation with MPOD in patients taking a statin may be useful for further investigation in this area.

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APPENDICES

APPENDIX A

RESEARCH SUBJECT INFORMATION SHEET

เอกสารชี้แจงข้อมูลแก่อาสาสมัครที่เข้าร่วมในโครงการวิจัย

(Research Subject Information sheet)

ชื่อโครงการวิจัย: ผลกระทบของ Atorvastatin ต่อค่า MPOD

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ชื่อผู้วิจัยร่วม) ทุกคน(: ผู้สนับสนุนทุนวิจัย: By Myself

ท่านได้รับการเชิญชวนให้เข้าร่วมในโครงการวิจัยนี้เนื่องจากท่านเป็น (ระบุเหตุผล).....

ก่อนที่ท่านจะตกลงใจเข้าร่วมหรือไม่ โปรดอ่านข้อความในเอกสารนี้อย่างถี่ถ้วน เพื่อให้ทราบถึงเหตุผลและรายละเอียดของ โครงการวิจัยนี้ว่า หากเข้าร่วม ท่านจะต้องทำอะไรบ้าง รวมทั้งข้อดีและข้อเสียที่อาจจะเกิดขึ้นในระหว่างการวิจัย

หากท่านมีข้อสงสัยใด ๆ กรุณาซักถามจากทีมงานผู้วิจัย ซึ่งจะเป็นผู้ตอบคำถามจนกว่าท่านจะเข้าใจอย่างชัดแจ้ง ท่านสามารถปรึกษาญาติพี่น้อง เพื่อน หรือแพทย์ที่ท่านรู้จัก ก่อนตัดสินใจว่าจะเข้าร่วมหรือไม่เข้าร่วมในโครงการวิจัยนี้

การเข้าร่วมในโครงการวิจัย จะต้องเป็น**ความสมัครใจ**ของท่าน ไม่มีการบังคับหรือชักจูง ถ้าท่านตัดสินใจเข้าร่วม กรุณาลงนามในเอกสารแสดงเจตนายินยอมเข้าร่วมโครงการวิจัยนี้

เหตุผลความเป็นมา และวัตถุประสงค์ของโครงการวิจัย

To compare the difference in MPOD value of hypercholesterolemic patients using statin and standard MPOD value.

เพื่อการเปรียบเทียบความแตกต่างของค่า MPOD ของผู้ป่วยไขมันในเลือดสูงโดยใช้ค่า statin และค่ามาตรฐานของ MPOD

ท่านได้รับเชิญให้เข้าร่วมในโครงการวิจัยนี้เพราะคุณสมบัติที่เหมาะสมดังต่อไปนี้

- Age between 40-60 years

  Patients who are taking Atorvastatin 10mg for at least 6 months

-อายุระหว่าง 40-60 ปี

  ผู้ป่วยที่ใช้ Atorvastatin 10 มก. เป็นเวลาอย่างน้อย 6 เดือน

ท่านไม่สามารถเข้าร่วมในโครงการวิจัย หากท่านมีคุณสมบัติดังต่อไปนี้

- Patients who are taking lutein and zeaxanthin supplementation
- Patients who are taking vitamin A and vitamin A related supplementation
- Patients with significant media opacity (corneal scar, cataract, vitreous haemorrhage)
- Patients with findings of age-related macular disease and other ocular diseases like cataract, glaucoma, optic atrophy and retinopathies, previous retina lasers or surgeries, previous ocular trauma
- Patients with serum cholesterol level >190 mg/dl
- Diagnosed Diabetes Mellitus or fasting blood sugar >126 mg/dl at first visit
- Patients with myocardial infarction, stroke
- Patients with liver dysfunction or renal impairment
- Patients with autoimmune disease, hyperthyroidism, hypothyroidism, or malignant tumours
- ผู้ป่วยที่ทานอาหารเสริมประเภท lutein and zeaxanthin
- ผู้ป่วยที่ได้รับวิตามินเอและอาหารเสริมที่เกี่ยวข้องกับวิตามินเอ
- ผู้ป่วยที่มีความผิดปกติดังต่อไปนี้ แผลเป็นที่กระจกตา,ต้อกระจก, เลือดออกในน้ำวุ้นตา
- ผู้ป่วยที่มีโรคจอประสาทตาที่เกี่ยวข้องกับอายุและโรคตาอื่นๆเช่นต้อกระจก, ต้อหิน,สายตาเสื่อมและจอประสาทตา, ทำการรักษาโดยเลเซอร์ ก่อนหน้าหรือการผ่าตัด, การบาดเจ็บของตาก่อนหน้า
- ผู้ป่วยที่มีระดับคอเลสเตอรอลในเลือด>190 mg/dl
- เป็นโรคเบาหวานหรือตรวจระดับน้ำตาลในเลือด>126mg/dl ในครั้งแรก
- ผู้ป่วยที่มีกล้ามเนื้อหัวใจตาย,โรคหลอดเลือดสมองหรือ
- ผู้ป่วยที่มีความผิดปกติของตับหรือไตเสื่อม
- ผู้ป่วยที่มีโรคภูมิแพ้ตัวเอง(autoimmunedisease), ไทรอยด์สูง(hyperthyroidism),ไทรอยด์ต่ำ(hypothyroidism) หรือโรคมะเร็ง

สถานที่ทำการวิจัย และจำนวนผู้เข้าร่วมในโครงการวิจัย

Research will take place to MFU university hospital.

การวิจัยจะเกิดขึ้นที่โรงพยาบาลมหาวิทยาลัย MFU

วิธีดำเนินการวิจัย

This is the observational cohort study. 22 males and females between 40-60 years of age, previously diagnosed with Hypercholesterolemia by the physicians and currently taking atorvastatin 10mg for at least 6 months were randomly selected as the volunteers.

นี่คือการศึกษาแบบสังเกตการณ์ อาสาสมัครชายและหญิง 22 คนอายุระหว่าง 40-60 ปีซึ่งเคยได้รับการวินิจฉัยว่าเป็นโรคไขมันในเลือดสูงโดยแพทย์และปัจจุบันได้รับยา atorvastatin 10 มก. อย่างน้อย 6 เดือน

ความไม่สุขสบาย หรือความเสี่ยงที่อาจเกิดขึ้น และการดูแลรักษา

Discomfort due to exposure to blue light during examination. But the blue light is used at the safe and only exposed for a short period of time level.

รู้สึกไม่สบายเนื่องจากการสัมผัสกับแสงสีฟ้าในระหว่างการตรวจ แต่แสงสีฟ้านั้นถูกใช้ในระดับที่ปลอดภัยและจะเปิดในช่วงเวลาสั้น ๆ เท่านั้น

ประโยชน์ที่คาดว่าจะได้รับจากโครงการวิจัย

For the patients taking atorvastatin for hypercholesterolemia, there will be enlightenment about the importance of macula pigment and continuing evaluation of maula pigment degeneration and age-related macular degeneration (AMD) risk.

1. For the public benefit, the screening of MPOD level is simple with shorter measurement time, non-hazard to ocular or vision, and relatively inexpensive for all standards.

2. For the field of biomedical research, this study will help to describe the association between reduced MPOD value and moderate use of atorvastatin in hypercholesterolemia since there are still limited and conflicting data concerning the variations of this association.

- สำหรับผู้ป่วยที่รับ atorvastatin สำหรับภาวะไขมันในเลือดสูงจะมีการเรียนรู้เกี่ยวกับความสำคัญของเม็ดสี macula และการประเมินผลอย่างต่อเนื่องของการเสื่อมสภาพของเม็ดสี maula และความเสี่ยงต่อ จอประสาทตาเสื่อม(macular degeneration: AMD)

1. เพื่อประโยชน์ต่อสาธารณะในการคัดกรองระดับ MPOD นั้นสะดวกรวดเร็วโดยใช้เวลาในการวัดที่สั้นกว่า และมีราคาไม่แพง ไม่เป็นอันตรายต่อตาหรือการมองเห็น

2. สำหรับงานวิจัยด้านชีวการแพทย์การศึกษานี้จะช่วยอธิบายความสัมพันธ์ระหว่างค่า MPOD ที่ลดลงกับการใช้ atorvastatin ในระดับปานกลางในภาวะไขมันในเลือดสูงเนื่องจากยังมีข้อมูลที่จำกัด และ มีข้อมูลที่ขัดแย้งกันเกี่ยวกับรูปแบบของการเชื่อมโยงนี้

ค่าใช้จ่ายที่ผู้เข้าร่วมในโครงการวิจัยจะต้องรับผิดชอบ

Participants will not be responsible for any expenses.

ผู้เข้าร่วมจะไม่เสียค่าใช้จ่ายใดๆ

การถอนตัวหรือการสิ้นสุดการเข้าร่วมในโครงการวิจัย

Patients with their own difficulty to undergo flicker sensitivity test .

ผู้ป่วยที่ทำการทอสอบแล้วไม่สามารถทำการทดสอบต่อได้หรือไม่พร้อมสามารถถอนตัวได้

การติดต่อ หากมีคำถามเกี่ยวกับการวิจัย

Principle investigator – Dr. Aye Chan Su Su, 2nd year student of Master of Science in Anti-Aging and Regenerative Medicine, School of Anti-Aging and Regenerative Medicine, Mae Fah Luang University

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Email address- summate.52@gmail.com

หากท่านได้รับการปฏิบัติที่ไม่เป็นธรรมในโครงการวิจัยนี้ ท่านสามารถติดต่อได้ที่ห้องปฏิบัติการคณะกรรมการจริยธรรมการวิจัยในมนุษย์ มหาวิทยาลัยแม่ฟ้าหลวง อาคารบริการ

วิชาการ (AS) ชั้น 4 มหาวิทยาลัยแม่ฟ้าหลวง โทรศัพท์ 053-917-170 ถึง 71 โทรสาร 053-917-170 หรืออีเมล rec.human@mfu.ac.th

APPENDIX B

INFORMED CONSENT FORM

หนังสือแสดงเจตนายินยอมเข้าร่วมโครงการวิจัย สำหรับอาสาสมัคร

(informed consent form)

ชื่อโครงการวิจัย …… ผลกระทบของ Atorvastatin ต่อค่า MPOD ….....

ข้าพเจ้า นาย/นาง/นางสาว..... ที่อยู่.....

ได้อ่านรายละเอียดจากเอกสารชี้แจงข้อมูลแก่อาสาสมัครผู้เข้าร่วมในโครงการวิจัยวิจัย ฉบับวันที่ .....

ข้าพเจ้าได้รับสำเนาเอกสารชี้แจงข้อมูลแก่อาสาสมัครผู้เข้าร่วมในโครงการวิจัย และสำเนาเอกสารแสดงเจตนายินยอมเข้าร่วมในโครงการวิจัยที่ข้าพเจ้าได้ลงนามและลงวันที่ ทั้งนี้ก่อนที่จะลงนามข้าพเจ้าได้รับการอธิบายโดยละเอียดจากผู้วิจัยถึงวัตถุประสงค์ วิธีการวิจัย ความไม่สุขสบายหรือความเสี่ยงที่อาจเกิดขึ้น ประโยชน์ที่คาดว่าจะได้รับจากการวิจัย และทางเลือกอื่น

ข้าพเจ้ามีเวลาและโอกาสเพียงพอในการซักถามข้อสงสัย โดยผู้วิจัยได้ตอบคำถามต่าง ๆ ด้วยความเต็มใจไม่ปิดบังซ่อนเร้นจนข้าพเจ้าเข้าใจเป็นอย่างดีแล้ว

ข้าพเจ้ารับทราบจากผู้วิจัยว่า หากเกิดอันตรายใด ๆ จากการวิจัย ข้าพเจ้าจะได้รับการรักษาพยาบาล ตามที่ระบุในเอกสารชี้แจงข้อมูลแก่อาสาสมัครผู้เข้าร่วมในโครงการวิจัย

ข้าพเจ้ามีสิทธิที่จะถอนตัวออกจากโครงการวิจัยเมื่อใดก็ได้ การถอนตัวนี้ไม่มีผลต่อการรักษาพยาบาลและสิทธิอื่น ๆ ที่ข้าพเจ้าจะพึงได้รับต่อไป

ผู้วิจัยรับรองว่าจะเก็บข้อมูลส่วนตัวของข้าพเจ้าเป็นความลับ การรายงานหรือสรุปผลการวิจัยจะไม่ระบุชื่อนามสกุลของข้าพเจ้า การเปิดเผยข้อมูลเกี่ยวกับตัวข้าพเจ้าต่อหน่วยงานต่างๆ ที่เกี่ยวข้อง จะกระทำด้วยเหตุผลทางวิชาการเท่านั้น

ข้าพเจ้าได้อ่านข้อความข้างต้นและมีความเข้าใจดีทุกประการแล้ว ยินดีเข้าร่วมในการวิจัยด้วยความสมัครใจ จึงได้ลงนามในเอกสารแสดงความยินยอมนี้

..... ลงนามผู้เข้าร่วมในโครงการวิจัย

(.....) ชื่อ-สกุล ผู้เข้าร่วมในโครงการวิจัย (ตัวบรรจง)

วันที่ .....เดือน.....พ.ศ.....

ข้าพเจ้าได้อธิบายโดยละเอียดถึงวัตถุประสงค์ วิธีการวิจัย ความไม่สุขสบายหรือความเสี่ยงที่อาจเกิดขึ้นประโยชน์ที่คาดว่าจะได้รับจากการวิจัย และทางเลือกอื่น ให้ผู้เข้าร่วมในโครงการวิจัยได้ทราบและมีความเข้าใจดีแล้ว พร้อมทั้งลงนามในเอกสารแสดงเจตนายินยอมด้วยความสมัครใจ

..... ลงนามผู้วิจัย

(.....) ชื่อ-สกุล ผู้วิจัย (ตัวบรรจง)

..... ลงนามพยาน

(.....) ชื่อ-สกุล พยาน (ตัวบรรจง)

วันที่ .....เดือน.....พ.ศ.....

APPENDIX C

QUESTIONNAIRES

Current History

Date.

Name ……

Age …… years

Gender Male / Female

ID number ……

Marital status Single / Married Occupation ……

Contact number ……

Education Primary/ Secondary/ Graduated/ Post-Graduated

Duration of taking Atorvastatin 10mg/day

Smoking (+) (-) Never

If (+), ……...years. Current/ Occasional/ Former/ Passive

Alcohol drinking (+) (-) Never

If (+), ...…..years. Daily/ Weekly/ Occasionally/ Former

Diet Fruits and vegetables servings (+) (-)

How many kinds per week

≥15 kinds of Fruits and vegetables per week (+) (-)

Oily fish intake (+) (-)

Eggs intake (+) (-)

How many eggs per week

Physical activity (+) (-) Never

If (+), Daily/ 3-5 times per week/ 1-2 times per week

Skin sensitivity to Ultraviolet light (+) (-)

Regular strong sunlight exposure or Outdoor working (+) (-)

……..hours/day

Sunbed use (+) (-)

Sunglasses use in bright conditions (+) (-)

Duration of mobile/computer/television screen usage per day (+) (-)

…..mins ….hours/

Eye Color - Black/ Dark brown/ Light Brown/ Grey/ Green/ Blue

Past Medical History

Hypertension (+) (-)

Heart Disease (+) (-)

Metabolic syndrome (+) (-)

Gout (+) (-)

Osteoarthritis (+) (-)

Dementia/ Alzheimer (+) (-)

Migraine (+) (-)

Glaucoma (+) (-)

Eye trauma (+) (-)

AMD (+) (-)

Cataract (+) (-)

Proliferative Diabetic Retinopathy (+) (-)

Diabetic Macula Odema (+) (-)

Past Surgical History

Any Operation to your eyes (+) (-)

Laser treatment or Surgical treatment Left/Right

Other major operation (+) (-) Why?

Other minor operation (+) (-) Why?

Family history

Diabetes mellitus (+) (-)
Father/ Mother/ Siblings

Any Complications with them Age-related macular degeneration (+) (-)
Father Mother Siblings

Hypertension (+) (-)
Father Mother Siblings

Drug History

Leutine and/or Zeaxanthin supplements (+) (-)
Multivitamin (+) (-)
Vitamin B (+) (-)
Vitamin C (+) (-)
Vitamin D (+) (-)
Vitamin E (+) (-)
Astaxanthin (+) (-)
Bilberry (+) (-)
Omega 3 Fish Oil (+) (-)
Lecithin (+) (-)
CoQ10 (+) (-)
Grape seed extract (+) (-)
Pine Bark extract (+) (-)
Rosehips (+) (-)
Other Supplements (+) (-)
Taking chloroquine, hydroxycholoroquine, ethambutol or tamoxifen (+) (-)
Any drug allergy (+) (-)

Case record form

Subject code…….

Date……

Age ..... years

Gender ……M/ F

MPOD Result……d.u.

CURRICULUM VITAE

CURRICULUM VITAE

NAME	Miss Aye Chan Su Su
DATE OF BIRTH	14 November 1993
ADDRESS	No. 80, Myittar Street, Thingangyun Township, Yangon, Myanmar

EDUCATIONAL BACKGROUND

2017	Bachelor of Medicine Bachelor of Surgery (M.B.B.S) University of Medicine Yangon, Myanmar

WORK EXPERIENCE

2017-Present	Medical Coordinator YIM Services
2016-2017	Internship Yangon General Hospital, West Yangon General Hospital and Central Women Hospital