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The effect of atorvastatin on macular pigment optical density: experimental study

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ABSTRACT

Introduction: Low-density lipoprotein (LDL)- and high-density lipoprotein (HDL) cholesterol are serum lipoproteins involved in the transportation of lutein and zeaxanthin to the retina to serve as macular pigments (MPs). Atorvastatin, a serum cholesterol-lowering agent, can affect the MP distribution and reduce macular pigment optical density (MPOD). MPOD is one of the best indicators of retinal diseases such as age-related macular degeneration. **Objective:** To study the effect of atorvastatin on the level of MPOD in people taking atorvastatin 10 mg for more than 6 months. **Methodology:** An experimental study was conducted on 44 Asian men and women, aged between 30 and 60 years and residing in Thailand, who were recruited and divided into two equal groups. The first group was currently taking atorvastatin 10 mg for at least 6 months, whereas the control group did not receive atorvastatin. MPOD was measured in all participants using the macular pigment screener-II. Participants were required to sign an informed consent form and complete questionnaires regarding various factors that may influence the MPOD. Data were analyzed using the Kolmogorov–Smirnov test and t-test to compare the MPOD between groups. **Results:** The mean MPOD of the experiment group was 0.3295 ± 0.1311 DU, whereas that of the control group was 0.4686 ± 0.1491 DU. The mean MPOD of the experimental group was significantly lower than that of the control group (p-value = 0.002). **Conclusion:** Patients taking atorvastatin had a lower MPOD than those who did not.

Keywords: *Macular pigment optical density, Hypercholesterolemia, LDL cholesterol, Atorvastatin*

Introduction

Hypercholesterolemia is a form of dyslipidemia that indicates an increased level of low-density lipoprotein cholesterol (LDL-C) in the serum. Compared to other middle-income countries in Asia, Thailand is among the countries with the highest unawareness rate regarding hypercholesterolemia at 78.0% in 2004, with a low level of treatment and control [1]. The Third Adult Treatment Panel (ATP III) states that different people have different cutoff levels of serum cholesterol depending on their cardiovascular risk levels [2]. In 2018, approximately 28.5 million adults (≥20 years) had total cholesterol levels ≥240 mg/dL with an overall prevalence of 11.9% globally [3]. The diagnosis of hypercholesterolemia is mainly based on fasting blood cholesterol levels. The National Cholesterol Education Program (NCEP) stated in the ATP III that an LDL-C level <100 mg/dL should be classified as the optimal level. A serum LDL-C level of 160–189 mg/dL is considered high, and >190 mg/dL indicates very high or severe hypercholesterolemia [4]. Table 1 shows the classification of LDL, high-density lipoprotein (HDL), and total cholesterol levels.

Table 1 ATP III classification of LDL- and total cholesterol [5]

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

High cholesterol levels can lead to the dangerous accumulation of cholesterol and other deposits on arterial walls, resulting in atherosclerosis, which reduces 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 have shown that serum cholesterol levels play a crucial role in cardiovascular disease-related mortality. It has also been claimed that a low dietary intake of fat and low serum cholesterol levels promote lower mortality from coronary heart disease and a lower risk for certain cancers [6]. According to the expert panel of various data analyses, clinical practice recommends the control of blood cholesterol levels to reduce the risk of atherosclerotic cardiovascular disease (ASCVD). Healthy diet and/or lifestyle modifications are recommended as standards of care in the management of blood cholesterol levels [7]. Controlling the related risk factors, such as hypertension and lifestyle changes, especially avoidance of smoking, should be adapted. The 2013 American Heart Association guideline on the treatment of blood cholesterol has classified statin therapy into high intensity, moderate intensity, and low intensity. One trial revealed that the crucial factor in reducing ASCVD events was the timely initiation of moderate-intensity therapy, which is targeted to lower LDL cholesterol by approximately 30.0% to <50.0%, or high-intensity statin therapy, which lowers LDL cholesterol by ≥50.0% [8].

Atorvastatin is one of the most commonly used statins, and its primary site of action is the liver, where the majority of both cholesterol synthesis and LDL clearance take place. It can effectively lower total cholesterol by 27.0%–37.9%, LDL cholesterol by 37.1%–51.7%, and triglycerides by 18.0%–28.3% when used within the recommended dosage range of 10–80 mg/day. The extent of LDL level reduction correlates with the dosage of atorvastatin used [9]. Atorvastatin has been proven to have higher efficacy and potency in lowering LDL cholesterol levels than simvastatin, which is commonly used in some countries [10].

The macular pigment (MP) protects the retina from oxidative damage by absorbing short-wavelength blue light, which is harmful to the eye [11]. It is mainly located in the fibers of Henle in the fovea and in the inner part of the parafoveal site [12-13]. The dietary hydroxy carotenoids lutein and zeaxanthin are the main components of MP [14]. The protective role of the MP in some ocular diseases, such as age-related macular degeneration, has been well studied [11, 15]. Several studies have investigated 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 values than that in men of the same age group [16-17]. Although the decline in MPOD with age is still questionable, older populations, particularly those aged ≥60 years, have been proven to have lower MPOD values than that in younger age populations [16]. A lower value was observed in people with a higher BMI [16-17]. Due to the lesser amount of melanin density present, the lighter iris color has a lower MPOD value [16-17].

MPOD measures the amount of blue light attenuation of the MP in the retina. It is directly related to the amount of integrated macular carotenoids, lutein and zeaxanthin, over the region of MP deposition. MPOD is usually described in optical density level or density units (DUs), and the normal range in the center of the macula is from 0 to 1 [19]. The central MPOD value >0.5 DU is considered high range; 0.5–0.25 DU, mid-range; and <0.25 DU, low range. The macular pigment screener-II (MPS-II), also known as MPS9000 (Figure 1), is a recently introduced device to measure MPOD for the screening and detection of ophthalmic diseases such as age-related macular degeneration [20].

Figure 1 The MPS-II device (L); the view through eyepiece (R)

The device has two test modes: (1) standard mode, which is a central test that estimates the MPOD value by comparing it with age normative data, and (2) detailed mode, which is a central plus peripheral test to determine the absolute MPOD value. The detailed mode is usually performed in patients who do not conform to age normative data, for example, patients with diabetes or those with other conditions that change the transmission of the ocular lens. In this study, only the standard mode was used in one eye.

Association of LDL cholesterol and transport of lutein and zeaxanthin

Circulating lipoproteins can be classified into six groups: very-low-density lipoproteins (VLDLs), intermediate-density lipoproteins (IDLs), LDLs, HDLs, 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 [21]. Lipoproteins are responsible for the transport of plasma carotenoids into the body. Fifty-five percent of total carotenoids are transported on LDLs, whereas 33.0% are associated with HDLs and only 10.0%–19.0% with VLDLs [22]. This finding suggests that MP may be influenced by the delivery and distribution of carotenoids to the retina by an individual's lipoprotein and lipoprotein profile in the blood [23].

Since the main effect of statins is the reduction in the serum cholesterol level, which is one of the main

factors in transporting MPs to the retina, patients taking long-term statin therapy are believed affect the MP distribution and, in turn, lower the MPOD value. Several studies have investigated the relationship between statins and MPOD. One study on simvastatin stated that MPOD was significantly lower with a longer duration of statin use [24].

Methodology

Study design and study population

An experimental study was conducted to compare the mean MPOD. A total of 44 volunteers were divided into two groups—experimental and control—with 22 participants in each group. The experimental group included patients aged 30–60 years who were currently taking atorvastatin for >6 months. The control group included healthy individuals within the same age range. Those who were using lutein and zeaxanthin supplementation were excluded from the study. Patients with age-related macular degeneration and other related ocular diseases such as glaucoma, cataract, optic nerve atrophy, diabetic retinopathy, previous lasers or surgery to the retina, and previous eye trauma were also excluded. Furthermore, patients with serum blood cholesterol >190 mg/dL and those with other comorbidities such as diabetes mellitus, myocardial infarction, stroke, liver dysfunction or renal impairment, autoimmune disease, hyperthyroidism, hypothyroidism, or malignant tumors were excluded from the study. Patients with difficulties in performing the flicker sensitivity test of the MPS-II were allowed to withdraw from the study.

Research procedure

Participants were divided into two groups: the experimental group, who received atorvastatin 10 mg for >6 months, and the control group, who did not receive atorvastatin. They were given a complete questionnaire to rule out the exclusion criteria. Questions were developed based on the factors that were related to the level of MPOD, such as participant characteristics, lifestyle, dietary habits, and environmental factors. Before conducting the MPOD measurement, instructions on how to perform the test on the MPS-II were explained to all participants. Each participant took approximately 60–90 s for the test to be done.

Ethical consideration and statistics

This study was approved by the Mae Fah Luang University Committee on Human Research in compliance with international guidelines such as the Declaration of Helsinki, the Belmont Report, the council for international organizations and medical science (CIOMS) guidelines, and the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use–Good Clinical Practice (COA: 171/2020). The MPS-II device is approved by the Thai Food and Drug Administration and has been proven to have little or no danger to the user during or after measurement. The results of the study were only provided to the participants and kept confidential. The patients participated voluntarily without any payment or charge on the tests and instruments. All volunteers had an equal chance of testing their MPOD levels.

The test results were analyzed using the SPSS (2016, IBM Corp., Armonk, NY, USA) software. Data were reported using frequency for categorical variables and mean and standard deviation for continuous variables. The Kolmogorov–Smirnov test was used to test the normal distribution, and the t-test was used to compare the MPOD values between the case and control groups.

Results

General characteristic of participants

The general demographic data of the 44 participants were recorded and analyzed using descriptive statistics (Table 2).

Table 2 Participants' demographic characteristics

Demographic	Experimental (n=22)	Control (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
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 (h/day)		
Mean ± SD	7.18 ± 2.11	8.36 ± 1.33
Min–max	4–10	6–10
Eye color, n (%)		
Dark Brown	12	13
Brown	10	9

The experimental group consisted of 12 males and 10 females with a mean age of 44.0 ± 9.8 years. Eight participants smoked, 8 participants used alcohol, and 8 participants engaged in physical activity. Furthermore, two participants had skin sensitivity, no participant was exposed to strong sunlight, and one participant regularly wore sunglasses. The mean screen use time was 7.1 ± 2.1 h/day. Most participants had dark brown color, and 10 had a brown color.

The control group consisted of 13 females and 9 males, with a mean age of 36.6 ± 6.4 years. Three participants smoked, 3 participants used alcohol, and 11 participants engaged in physical activity. None of the participants had skin sensitivity, was exposed to strong sunlight, and wore sunglasses regularly. The mean screen use time was 8.3 ± 1.3 h/day. Most participants had a dark brown color, and 9 were brown in color.

Table 3 Underlying disease and treatments apart from hyperlipidemia

Factor	Experimental	Control
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	0 (0.0%)	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 macular edema	0 (0.0%)	0 (0.0%)
Operation/treatment to the eye, n (%)		
Other major operation	3 (13.6%)	0 (0.0%)
Other minor operation	3 (13.6%)	0 (0.0%)

A family history of hypertension (n = 8), diabetes mellitus (n = 8), and heart disease (n = 4) was noted; three participants had gout, and one had osteoarthritis. Other major operations (n = 3) and other minor operations (n = 3) were performed, and no surgery or treatment of the eye in any participant. For those in the control group, a family history of diabetes mellitus and hypertension in 7 and 1 participant, respectively. None of the participants underwent surgery or treatment of the eye or other major and minor operations (Table 3).

Sixteen participants eat fruits and veggies, 14 eat eggs, and 12 eat oily fish. The participants were found to take omega-3 fish oil (n = 13), vitamin C (n = 12), vitamin D (n = 8), astaxanthin (n = 6), CoQ10 (n = 5), multivitamins (n = 1), and other supplements (n = 1). An equal number of participants took medications for <12 months (n =11) and ≥12 months (n =11). In the control group, 17, 16, and 16 participants were found to eat oily fish, fruits and veggies, and eggs, respectively. The participants were found to take vitamin C (n = 14), omega-3 fish oil (n = 8), multivitamins (n = 7), vitamin D (n = 7), CoQ10 (n = 3), vitamin B (n = 2), and astaxanthin (n = 2) (Table 4).

Table 4 Supplements and medications

Factors	Experimental (n=22)	Control (n=22)
Fruits and veggies	16	16
Eggs	14	16
Oily fish intake	12	17
Lutein and zeaxanthin	0	0
Multivitamin	1	7
Vitamin B	0	2
Vitamin C	12	14
Vitamin D	8	7
Astaxanthin	6	2
Omega-3 fish oil	13	8
CoQ10	5	3
Other supplements	1	0
Duration of taking atorvastatin 10 mg/day		
<12 months	11	–
≥12 months	11	–

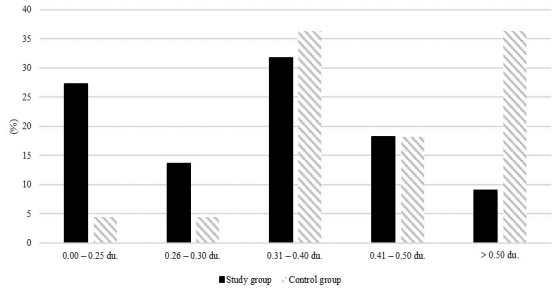

Figure 2 The comparison of MPOD values between groups

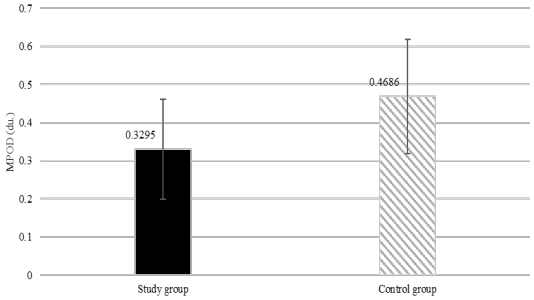

Figure 3 The comparison of MPOD values between groups

Figure 2 show the results of the MPOD comparisons of participants who received atorvastatin 10 mg for at least 6 months in the experimental and control groups.

In the experimental group, the MPOD level was 0.26–0.50 DU (mid-range) in 14 participants, followed by 0.00–0.25 DU (low-range) in 6 and >0.50 DU (high

range) in 2. In the control group, the MPOD level was 0.26–0.50 DU in 13 participants, followed by >0.50 DU in 8 and 0.00–0.25 DU in 1.

The mean MPOD in the experimental group was 0.32 ± 0.13 DU (min–max, 0.05–0.58). For the control group, it was 0.46 ± 0.14 DU (min–max, 0.24–0.86). Comparing the MPOD between the experimental and control groups, the mean MPOD in the experimental group was significantly lower than that in the control group (p-value = 0.002). A significant reduction in MPOD levels was observed in patients taking atorvastatin 10 mg for at least 6 months (Table 5 and Figure 3).

Table 5 Statistical analysis of MPOD between groups

Group	n	Mean	SD	Min–max	t	df	p-value
Experimental	22	0.32	0.13	0.05–0.58	−3.285	42	0.002*
Control	22	0.46	0.14	0.24–0.86			

p-values are determined using the independent t-test.

*p-values = 0.05 were considered statistically significant.

Discussion

Our findings were consistent with those of a previous study showing that MPOD was significantly lower in patients using statins for >1 year than that in non-statin users [25]. Moreover, one study revealed that patients using atorvastatin had lower MPOD values than that in simvastatin users, suggesting that the type of statin and the duration of treatment play a significant role in the MPOD values. This may explain the controversial point from a previous study conducted in patients receiving simvastatin, in which the results showed no significant difference in MPOD in patients taking simvastatin 10 mg for 6–12 months and normal patients [24].

A previous study showed that MPOD values were influenced by several physical and environmental factors such as age, sex, BMI, eye color, diet, physical activity, and amount of screen time or exposure to blue light [26]. MP density also showed correlations with lutein and zeaxanthin in relation to serum lipid levels [26].

Serum lipoproteins, especially LDL, are one of the main components of the transport of carotenoids to the retina as MPs. Atorvastatin, a lipid-lowering agent that can reduce LDL by 37.1% to 51.7% in the blood, possibly decreased the distribution of MPs, leading to a reduction in MPOD value. Decreased MPOD value can cause decreased visual acuity, less contrast sensitivity, slower glare recovery, and reduced light sensitivity and is an important risk factor for age-related macular degeneration, which can cause irreversible blindness. A comparative study between atorvastatin and simvastatin showed that atorvastatin is more potent and effective than simvastatin [10].

Therefore, it is advantageous for patients taking statin drugs to be aware of the risk of macular degeneration and blindness. Health education on eye care should be provided to all patients on long-term statins such as eating lutein- and zeaxanthin-rich foods, including green leafy vegetables, carrot, pumpkin, corn, and eggs, or taking lutein and zeaxanthin supplementations. Regular eye check-ups including MPOD measurements should be performed for the early detection of reduced MPOD values and prevention of age-related macular degeneration.

Conclusion

The mean MPOD in patients using atorvastatin 10 mg for at least 6 months (0.32 ± 0.13 DU) was significantly lower than that in the control group (0.46 ± 0.14 DU). The duration of medication administration in the experimental participants taking atorvastatin 10 mg varied from 6 months to 20 years. Assessment of the risk associated with long-term statin use will be beneficial, including a controlled, prospective clinical trial with exact dietary and/or lifestyle modifications and supplemental trials, and further investigations on the serial measurement of serum lutein and zeaxanthin and MPOD in patients taking statins are necessary.

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