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Review Article

Macular Pigments Optical Density: A Review of Techniques of Measurements and Factors Influencing their Levels

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Abstract

Of the numerous carotenoids found in nature, lutein, zeaxanthin and meso-zeaxanthin are deposited in the retina, specifically the macula. These xanthophylls are associated and correlated with healthy and disease states such as Age Related Macular Degeneration (ARMD). The age of the patient, dietary intake and other health factors influence the density of these macular pigments which can be measured using various techniques. The level of Macular Pigment Optical Density (MPOD) can also be influenced by oral supplementation of various carotenoids; although, further research is needed to establish the significance of oral supplementation as treatment regimes.

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- Motion photometry
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- Fundus autofluorescence
- Raman spectroscopy

INTRODUCTION

Macular pigments are composed of three carotenoids, lutein, zeaxanthin and meso-zeaxanthin [1-3]. There are 14 carotenoids detected in serum, however, lutein and zeaxanthin contain hydroxyl groups at the end of each molecules, which makes them biochemically distinct from the other carotenoids and thus are called xanthophylls [2,3]. They are found in the retina, specifically the macula and are responsible for the fovea's yellow coloration [4,5]. They are at higher concentrations at the center of the macula, in the axons of the photoreceptors and inner plexiform layers of the retina [2,4,6]. Their concentration decreases 100-fold when moved a few millimeters to the periphery, where lutein is more prevalent than zeaxanthin 2.4:1 [2,7]. This difference in concentration of both pigments correlates with the rod-cone ratio [2,7]. Meso-zeaxanthin which is believed to be a biochemical conversion of xanthophyll is a carotenoid present in across the macula [2,8,9].

This report will review the literature related to factors that influence the level of Macular Pigments Optical Density (MPOD), protective effect of MPOD on ocular health and the various measurement techniques that can be utilized to measure MPOD.

Factors contributing to level of MPOD

Macular carotenoids are associated in maintaining the health of the retina and thus visual performance [4,5,10]. With the exception of meso-zeaxanthin [2,8], they can only be acquired through dietary intake, either from supplements or food such as vegetables, spinach, corn, and egg yolks [2,10]. Certain dietary habits like that of the Chinese have a relatively higher dietary intake of lutein and zeaxanthin when compared to the diet of individuals in the Western part of the world [11-13].

Research on macular pigments can be assessed using a variety of in-vitro and in-vivo techniques. Several studies have investigated association and correlations between MPOD and social factors such as sex, age, Body Mass Index (BMI) and iris color. Although, the findings are not overwhelmingly unanimous, overall, males in specific age groups have higher MPOD compared to females [14,15]; evidence ranging from a 13% to 38% difference with one study finding no difference at all [4]. The difference of MPOD levels between males and females could be due to the carotenoid-lipid transport system, which is hormonally controlled as well as the influence of steroid hormones [4,16].

There appears to be a decline in MPOD values with an increase in age, particularly in individuals 60 years and higher [14]. There has been an inverse relationship between BMI and MPOD such that those individuals with higher BMI tend to have lower levels of MPOD [14,17]. This may in part be due to the fact that carotenoids are stored in fat. An individual with greater body fat content may be storing more carotenoids in their body fat, hence lower levels are deposited in the macula region. The storage of carotenoids in fat could also serve as an explanation of why females have a lower MPOD level than males; females are

known to have higher percentage of body fat [4,16]. The level of BMI co-vary with dietary habits and thus may also explain the association between BMI and MPOD [14,18].

Prior work has shown an association between iris color and MPOD [14,18]. Iris color is based on the amount of ocular melanin, lighter color irises will have less melanin density and will increase transmission of light to the retina [18]. Evidence indicates that a lighter iris color is related to a lower MPOD [14,18]. However, this relationship is not so clear since both pigments share similar environmental pressures [18]. Increased light transmission could lead to increased oxidative stress in both melanin and macular pigments leading to their depletion [14,18].

Protective effect of MPOD on ocular health

The macular carotenoids may protect the retina; and specially the macula by two proposed functions: 1) as a filter to blue light and 2) decreasing oxidative stress. Blue light has short wavelengths thus is highly energetic causing the production of excessive amounts of reactive oxygen species in retina [2]. The MPOD may decrease the amount of blue light reaching the photoreceptor cells since they have an absorption spectrum of 400-450 nm, (peak around 460 nm); making them likely to serve as a blue-light filter [2,10,19]. Second, these pigments may be protecting the macula from oxidative stress by neutralizing such reactive oxygen species by acting as antioxidants in the inner retina and photoreceptor RPE complex [2,10,19].

The MPOD's ability to act as a filter of blue light and decrease oxidative stress has led researchers to think that levels could help protect individuals from developing eye diseases such as age-related macular degeneration (ARMD [10,19]. ARMD is a leading cause of vision related issues. It is estimated that ARMD cause of 54.4% of the visual impairment and 22.9% of blindness among Caucasians [2,18]. It is predicted by the year 2020 there will be a two-fold increase in the cases of ARMD [2,5]. It has been shown that healthy individuals have higher MPOD levels than ARMD patients [2,20]; thus ARMD progression could be related to a low level of macular pigments. Other diseases that correlate with low MPOD levels are Stargardt macular dystrophy [2], glaucoma and retinitis pigmentosa [21]. Prior reports have shown that oral supplementation of carotenoids can increase the level of MPOD [21,22].

Effect of oral supplementation on MPOD

The Caucasian population has a higher prevalence of AMD compared to other populations such as the Chinese and Asian Indians. This could be partly due to the higher intake of carotenoids in the diet [12,13]. Evidence so far has shown varying degrees of success of carotenoid supplementation [21,22]. Studies have shown that oral supplementation of carotenoid not only increases MPOD levels but also improves visual performance under glare conditions [21,22]. The LUTEGA study by Dawczynskietal., demonstrated that dietary supplementation over 1 year increased the levels of lutein and zeaxanthin in the macula [23] thus implying that AMD patients can benefit from a long term oral supplementation of these pigments [23].

Techniques to measure macular pigment optical density

Given that levels of MPOD are associated with various diseases it will be useful to obtain a measure of MPOD which is repeatable and reliable. Further it may have a role in monitoring changes and treatment efficacy in patients with ARMD.

Currently, macular pigments can be measured by in vitro and in vivo mechanisms. In vitro methods such as High-Pressure Liquid Chromatography (HPLC) and microdensitometry can only be used on excised retinas [5,10] not in humans. To measure macular pigment levels clinically, we can use non-invasive techniques, which are categorized as psychophysical or objective [5,10]. The difference relies in that psychophysical techniques require participation from the subject, whereas objective techniques require minimal involvement from the subject [5,10]. There are five types of psychophysical techniques used to measure macular pigments levels. We will be discussing the two most commonly used techniques, motion photometry and heterochromatic flicker photometry.

Psychophysical techniques

Heterochromatic Flicker Photometry (HFP) has replaced most of the other psychophysical techniques. Some advantages of the heterochromatic flicker photometry are relative ease of testing and the shorter measurement time [5,10]. The mode of action of heterochromatic flicker photometry is based on the macular pigment's absorption spectrum at the retina, specifically the macula and fovea [5,7,10]. The heterochromatic flicker photometry determines the MPOD by displaying two light stimuli of different wavelengths, which the patient perceives as a flicker [7,10]. The light stimuli alternates between a blue light of short wavelength, which is maximally absorbed by the macular pigments, and a green-yellow light of longer wavelength, which the pigments do not absorb [7,10]. First, the flickering light is targeted to the fovea; upon perceiving the stimulus the subject will respond that "the target is flickering". The machine alters the amount of blue and green light until the patient reports minimal flicker [5,10]. Then, the same process is repeated but at the parafovea location where there is minimal macular pigments [5,10,19]. The time taken to obtain the foveal measurement is greater than the parafoveal measurement as there is a great density of carotenoid at fovea [7,10]. The MPOD is estimated as at the log ratio of the radiance of blue light needed at the fovea compared to the parafovea [10]. Current heterochromatic flicker photometry devices such as MPS 9000 and QuantifiEYE [7,19] have modified the subject's input during the test, instead of the subject responding until minimal flickering is perceived, they respond to the appearance of a flickering light [19,24]. The patient reports flickering of light at central location. The machine alters the radiance of blue light versus the green-yellow light until the patient perceives no flicker and is recorded as the lowest point on the graph given below (Figure 1). The machine continues to increase the blue radiance until a flicker is perceived three times consecutively. The machine has a built in correction factor to account for the age related yellowing of the lens and a final MPOD measurement is obtained. If the person has an intraocular lens implantation post cataract surgery the fellow un-operated eye should be measured. If both eyes have an intraocular lens then the age of patient is recorded as 21 years when the machines correction factor is zero [1].

The main advantage of heterochromatic flicker photometry use is that there is no need for pupillary dilation, the device is

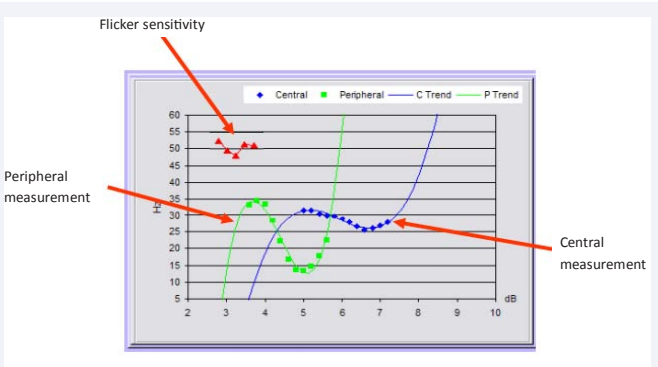

Figure 1 QuantifEye graph. The central graph should have a flat "S" on its side shape. For the graph to be acceptable it needs to have a clearly defined minimum reading with three consecutive higher (UP) readings[1].

relatively inexpensive, and the repeatability and validity of MPOD measurements is proven [5,7,10]. However, in certain situations, patients are not able to perceive the flickering light and this device is not suitable for the study of young children and/or people with poor visual acuity [5,7,10].

Motion Photometry

Motion photometry is similar to heterochromatic flicker photometry; both techniques utilize two light sources with different wavelengths [5,10,25]. However, motion photometry uses the light stimuli to illuminate the bars of moving square wave gratings. The intensity of the light is adjusted until the moving squares slows down or changes direction [10,25]. As in the heterochromatic flicker photometry technique, the test is performed at the fovea and at a parafoveal location. The MPOD peak measurement is calculated by taking the log ratio of the differences in intensity between the stimuli perceived at fovea and parafovea [10,25].

Objective techniques

Fundus Reflectometry: Fundus reflectometry measures MPOD on the basis of light reflected from the retina and the choroid [10,26]. Fundus reflectometry utilizes light of two wavelengths one that is absorbed by the macular pigments (blue spectrum) and another that is not absorbed by the pigments. Fundus reflectometry has two main methods; The first one is a comparison of reflection of light at central and peripheral regions [10]. The second method is based on spectral analysis, which involves analyzing the spectrum of the reflected light form a specific region on the retina [5,10].

Unlike heterochromatic flicker photometry, fundus reflectometryis an objective method of measurement and thus may obtain MPOD estimates in pediatric and special needs population [10]. Fundus reflectometry is also proven to be repeatable and estimates of MPOD can be obtained in short duration [5,10]. However, fundus reflectometry does require pupillary dilation as well as the need for precise alignment before the measurements are obtained. Compared to the heterochromatic flicker photometry, fundus reflectometry is relatively expensive and the technique and instrumentation require higher level of understanding and training to obtain measurements [5,10].

Fundus Autofluorescence: Fundus autofluorescence is another objective techniques to measure MPOD invivo. It is based on the intrinsic fluorescence or autofluroescence of lipofuscin [5,27], a waste product that accumulates with age on the Retinal Pigment Epithelium (RPE) [10]. Lipofuscin is the main fluorophore in autofluroescence and will fluoresce when excited with light wavelengths between 400-590 nm. The absorption spectrum of lipofuscin is similar to the absorption spectrum of the macular pigments (400-540nm) [5,10,27]. Macular pigments are located in the axons of the photoreceptors and inner plexiform layers of the retina which is anterior to the location of lipofuscin in the retinal pigment epithelium. The lipofuscin fluorescence will be lesser in eyes with greater macular pigments and greater in eyes with decreased macular pigments [10]. MPOD values are calculated by the measuring the difference of autofluroescence emitted from the fovea and parafovea [10,27].

An advantage of fundus autofluorescence includes an objective measurement technique, good reliability when retesting and it can be applied to a diverse population, including children [5,10]. However, some of the disadvantages include the need for pupillary dilation as well as the discomfort of photopigment bleaching [5,10].

Raman spectroscopy: Raman Spectroscopy is the newest technique developed for MPOD measurement [10]. When a monochromatic light is directed through any molecule it will result in two types of light scattering: 1) elastic 2) inelastic [10]. The inelastic scattering causes a shift in the wavelength of the incident light, known as Raman shift, which is molecule specific [10,28]. When the incident wavelength is similar to the absorption spectrum of the molecule there is an enhancement of the Raman shift thus allowing for the molecule to be identified [10]. Raman spectroscopy can be used to identify the macular pigments since these exhibit five orders of magnitude of resonance enhancement upon excitement by 488 nm of argon laser light [5,10].

This technique has gained approval by researchers since it is the only technique that measures the pigments themselves instead of measuring the pigments indirectly by analyzing other structures [28]. One of the main advantages of this technique is that it is sensitive and specific for macular carotenoids and can be used in subjects with low visual acuity [10,29]. Some disadvantages are that there is a need for pupillary dilation and the need for highly specialized and expensive devices [10,29].

Low levels of MPOD have shown association with different disease states and there is evidence that MPOD levels can change with oral supplementation. However, because of the multifactorial nature of disease, the efficacy of carotenoid supplementation is still to be unequivocally proven. Further research is needed in this area to establish treatment regimens and protocols of carotenoid supplementation, and to determine when and how to use MPOD values clinically to identify and monitor disease progression.

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