学 位 論 文 の 要 旨

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学 位 論 文 名	Comparison of Macular Pigment and Serum Lutein Concentration Changes Between Free Lutein and Lutein Esters Supplements in Japanese Subjects
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論 文 内 容 の 要 旨

INTRODUCTION

In 1980s, macular pigment was defined chemically as a mixture of two carotenoids, lutein and zeaxanthin, which are concentrated in the macula lutea, absorb blue light, and act as a filter that may attenuate photochemical damage caused by short-wavelength visible light (blue light). These carotenoids are also antioxidants that may protect against light-induced oxidative damage in the retina by quenching oxygen radicals.

Age-related macular degeneration (AMD) is a multifactorial disease, and oxidative stress caused by short wavelength blue light is considered an important factor in the disease. Since macular pigment protects against the blue light hazard, numerous studies of macular pigments and AMD have been undertaken. Some studies have found that MPOD levels in AMD eyes were significantly lower than in normal eyes, and our previous study in a Japanese population suggested that lower MPOD levels may be a risk factor for AMD progression. The ability of lutein and zeaxanthin supplements to prevent AMD has been investigated and a large clinical study recommended antioxidant supplements containing lutein and zeaxanthin.

Humans cannot synthesize lutein in the body; it must be obtained from ingestion of vegetables and fruits or supplements. Lutein can be present in fruits and vegetables both in the free form and the more stable fatty acid esterified form. Some investigators have suggested that the absorption rate in the intestine differs between free lutein and lutein esters, and some studies showed different serum lutein concentrations and MPOD levels after supplementation of free lutein and lutein esters. Bowen et al. reported that the serum lutein concentrations in subjects taking lutein esters supplementation were higher than in those taking free lutein and concluded that the lutein esters form was more bioavailable than the free lutein. In contrast, Norkus et al.

reported that the serum lutein response was higher with free lutein than with lutein esters. Few reports have been published about the response of the MPOD levels to lutein supplementation compared with each type of lutein. Therefore, it remains unclear which type of lutein supplementation increases the MPOD levels. In the current study, we investigated the response in the serum lutein concentrations and MPOD levels to two forms of lutein in healthy Japanese individuals. This is not a study to prove the equivalence of both forms.

MATERIALS AND METHODS

The study protocol was approved by the Ethics Committee of Shimane University and written informed consent was obtained from all subjects. Twenty healthy Japanese subjects who ranged in age from 22 to 47 years (8 men, 12 women) were recruited into this prospective, randomized, doubled-blind study and received either 10 mg of oral free lutein (n = 10) or 20 mg of lutein esters equivalent to 10 mg of free lutein (n = 10) daily for 3 months. The best-corrected logarithm of the minimum angle of resolution visual acuity (logMAR VA) and refractive error of each individual were measured at baseline and 3 and 6 months after the start of supplementation. Subjects underwent contrast and glare sensitivity testing, using a contrast glare-tester at the three time points. The serum lutein concentration and MPOD levels were measured at the three time points.

RESULTS AND DISCUSSION

Subject age, sex, spherical equivalent refractive error, serum lutein concentrations, and MPOD levels did not differ significantly between the groups at the base line. The mean logMAR VA was -0.08 ±1.46 in free lutein group and -0.13±0.08 in lutein ester group, which did not differ significantly. The logMAR VA was stable throughout the study and no significant changes were seen in both groups 3 and 6 months after the start of supplementation. Three and 6 months after the start of supplementation, there were no significant differences in contrast and glare sensitivities across all targets, except for the glare sensitivity at 4.0 degrees in the lutein esters group 6 months after supplementation.

The mean baseline serum lutein concentrations were 3.7±1.05 μmol/L in the free lutein group and 3.2±1.21 μmol/L in the lutein esters group, which did not differ significantly. Three months after the start of supplementation, the serum lutein concentrations increased to 6.4 ±2.98 μmol/L in the free lutein group and to 5.7±1.63 μmol/L in the lutein esters group, both of which differed significantly from baseline. At 6 months, i.e., 3 months after the end of supplementation, the serum lutein concentrations decreased to 4.2 ± 1.02 μmol/L in the free lutein group and to 4.0 ± 1.30 μmol/L in the lutein esters group. At 3 months, the rate was 89% in the free lutein group and 97% in the lutein esters group, which did not differ significantly.

The increasing MPOD levels in the free lutein group were 38% at 3 months, which differed significantly from baseline. At 6 months, i.e., 3months after the end of supplementation, the increasing MPOD levels were 47%, which differed significantly from baseline. In the lutein esters group, the increasing MPOD levels at 3 months were 17% and did not differ significantly from baseline, but the increasing MPOD levels were 50% at 6 months. This was significantly

higher than at baseline and at 3 months.

The serum lutein concentrations increased 3 months after supplementation in both the free lutein and lutein esters group and the increasing levels did not differ between the two groups. The bioavailability of free lutein and lutein esters is not fully understood, and some studies have reported different effects on the increases in the serum lutein concentrations. In the current study, however, there was no significant difference between the two supplements that contained the same amount of free lutein. This result suggested that esterification did not affect intestinal absorption. Three months after cessation of the supplements, the serum lutein concentrations decreased in both groups. Landrum et al. also reported this rapid decrease. Lutein is generally stored in adipose tissue but not in the blood.

The MPOD levels at 6 months were higher than at 3 months in both supplement groups, although the serum lutein concentrations decreased. These results suggested that the MPOD levels keep increasing for some period after supplementation stopped. Several studies have reported the tendency for a post-supplementation increase in the MPOD levels. Wang et al. reported that lutein was selectively retained in the retina of chicks receiving a xanthophyll-free diet for 28 days; in contrast, the lutein concentrations in the plasma and other tissues decreased up to 90% of their original level. Some mechanisms have been considered. Landrum et al. suggested a very slow turnover of carotenoids in the retina and a possible specific mechanism to maintain the MPOD levels in the retina. Li et al. reported that the binding affinities between human β, β-carotene-9', 10'-dioxygenase (BCO2) and lutein, zeaxanthin, and meso-zeaxanthin were 10- to 40-fold weaker in humans than in mice (In Vitro). BCO2 is a xanthophyll carotenoid cleavage enzyme. The inactivity of BCO2 in humans may induce lengthy preservation of lutein in the retina. Generally, adipose tissue is a major storage organ of carotenoids. Johnson et al. examined the relationships among the lutein concentration in serum and adipose tissue and the MPOD levels in subjects with addition of spinach (60 g/day) and corn (150 g/day) to the diet for 15 weeks. After cessation of the dietary modification, lutein concentration in the adipose tissue decreased, while the MOPD levels remained high. The authors suggested that macular pigment in the retina might be supplied from lutein stored in adipose tissue.

This study was not designed to determine the equivalence of the two lutein supplements. A more detailed investigation with more subjects is needed to prove the effects of free lutein or lutein esters.

CONCLUSION

In the current study, serum lutein concentrations increased significantly 3 months after supplementation with either free lutein or lutein esters, and no significant differences were detected between the two. The MPOD levels significantly increased 6 months after supplementation began with both free lutein or lutein esters. Both forms of lutein were considered useful for supplements to increase macular pigments that are useful to prevent development of AMD.

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論文審査の結果の要旨

黄斑色素は霊長類の黄斑部に存在し、カロテノイドの一種であるルテイン、ゼアキサンチン、メソゼアキサンチンから構成される。中心窩には特にメソゼアキサンチンが多く，周辺部になるにつれてルテインの割合が高くなる。ルテインとゼアキサンチンは460 nm に吸収ピークがあり、青色光を効率良く吸収し、錐体細胞に過度の青色光が到達しないように働くほか、一重項酸素を還元するなど抗酸化作用を有する。

加齢黄斑変性症は高齢者の失明の主要な原因であり、短波長の光による酸化ストレスが主要な原因とされている。ヒトは体内でルテインを合成できないため、食事やサプリメントとして体内に取り入れる必要がある。ルテインにはフリー型とエステル型が知られているが、フリー型・エステル型を内服後の血清ルテイン濃度や黄斑色素密度の変化について、どちらがより効果的なのかははっきりとわかっていない。特にこれまでの報告は欧米人で行われており、アジア人で行われた報告はない。そこで今回、健康な日本人20人を対象にフリー型ルテインとエステル型ルテインを3ヵ月間内服させ、血清ルテイン濃度と黄斑色素密度の変化について検討した。その結果、血清ルテイン濃度は投与開始後3ヵ月目に両群ともbaselineより有意に増加し、 その増加はフリー型1.89倍、エステル型1.97倍であった。この血清ルテイン濃度は投与開始6ヵ月目に両群ともに低下し、両群の間に有意差はみとめられなかった。一方、黄斑色素密度は投与開始後3ヵ月目に両群とも増加し、その増加はフリー型では1.38倍、エステル群は1.17倍であった。興味深いことに投与開始から6ヵ月目、すなわち投与終了から3ヵ月たっているにも関わらず、フリー型はbaselineと比較して1.47倍、エステル型は1.50と両群とも有意に増加していた。両群の間に有意な差は認められなかった。以上の結果から、フリー型ルテイン、エステル型ルテインともに黄斑色素を増加させるのに有用なサプリメントであることが確認され、ルテインの内服は加齢黄斑変性の進行予防に有益である可能性が示唆された。本研究は今後のルテインの臨床応用に重要な知見をもたらすものであり、博士(医学)の学位授与に値すると判断した。