Lutein and zeaxanthin intakes and risk of age-related macular degeneration and cataracts: an evaluation using the Food and Drug Administration’s evidence-based review system for health claims

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ABSTRACT
The labeling of health claims that meet the significant scientific agreement standard and of qualified health claims on conventional foods and dietary supplements requires premarket approval by the Food and Drug Administration (FDA). The FDA conducts an evidence-based review to ascertain whether sufficient evidence exists to support a significant scientific agreement standard or a qualified health claim. The FDA recently reviewed intervention and observational studies that evaluated the role of lutein and zeaxanthin in reducing the risk of age-related macular degeneration and cataracts. On the basis of this evidence-based review, the FDA concluded that no credible evidence exists for a health claim about the intake of lutein or zeaxanthin (or both) and the risk of age-related macular degeneration or cataracts. Am J Clin Nutr 2006; 84: 971–4.

KEY WORDS Lutein, zeaxanthin, age-related macular degeneration, cataracts, health claims

INTRODUCTION
Age-related macular degeneration, cataracts, lutein, and zeaxanthin

Two types of age-related macular degeneration (AMD) exist—“dry” and “wet.” Approximately 85–90% of AMD cases are dry AMD, which is characterized by a deterioration of the retina that is associated with the formation of small yellow spots (drusen) under the macula. This phenomenon leads to a thinning and drying out of the macula, which in turn lead to a loss of macular function and result in a gradual loss of vision. Dry AMD can progress to wet AMD when new blood vessels are formed to improve the blood supply to oxygen-deprived retinal tissue. The development of new blood vessels results in hemorrhage, swelling, and scar tissue.

Dry AMD has 3 stages: early AMD, which involves several small or a few medium-sized drusen; intermediate AMD, which involves either many medium-sized or ≥1 large drusen; and advanced AMD, which involves both drusen and a blurred spot in the center of the vision. Age-related maculopathy is characterized by abnormalities in the macular area, and the symptoms of late age-related maculopathy are similar to those of AMD (1). Cataracts are a clouding of the lens (greater optical density of the lens) in the eye that affects vision. If the lens is cloudy from a cataract, images will appear blurred. A cataract can occur in one eye or both eyes, and they can form because of clumping of protein on the lens, coloration of the lens to a brownish shade that can occur with age, or the presence of certain diseases such as diabetes. Most cataracts are age-related.

The lens and macular pigment of the retina contain the carotenoids lutein and zeaxanthin, which have been shown to have antioxidant properties (2). The macular pigment is an effective filter of damaging blue light, which causes retinal injury. The cause of cataracts is multifactorial, including oxidative stress (3). An age-related inverse relation has been reported for macular pigment density and lens density (4). Therefore, it has been hypothesized that increasing the intakes of lutein and zeaxanthin may inhibit the onset of AMD and age-related cataracts.

Health claims

The Nutrition Labeling and Education Act of 1990 authorized the FDA to allow the labeling of conventional foods and dietary supplements with statements that describe the relationship between a substance (food or food component) and a disease (eg, AMD, cataracts, cancer, and cardiovascular disease) or health-related condition. This relationship is called a health claim. A health-related condition (eg, hypertension) is a condition that is essentially indistinguishable from a disease (eg, coronary heart disease), is a surrogate marker for risk of a specific disease (eg, serum cholesterol concentrations for coronary heart disease), or both. Health claims were first authorized under the significant scientific agreement (SSA) standard. The SSA standard is a rigorous standard that requires a high level of confidence in the validity of a substance-disease relationship (5). Because of court decisions dealing with health claims for dietary supplements that raised First Amendment issues and because of a major initiative on qualified health claims that was introduced by the FDA in 1997, health claims were redefined under the qualified health claims standard (5). The SSA standard is a rigorous standard that requires a high level of confidence in the validity of a substance-disease relationship (5). Because of court decisions dealing with health claims for dietary supplements that raised First Amendment issues and because of a major initiative on qualified health claims that was introduced by the FDA in 1997, health claims were redefined under the qualified health claims standard (5). The SSA standard is a rigorous standard that requires a high level of confidence in the validity of a substance-disease relationship (5). Because of court decisions dealing with health claims for dietary supplements that raised First Amendment issues and because of a major initiative on qualified health claims that was introduced by the FDA in 1997, health claims were redefined under the qualified health claims standard (5). The SSA standard is a rigorous standard that requires a high level of confidence in the validity of a substance-disease relationship (5). Because of court decisions dealing with health claims for dietary supplements that raised First Amendment issues and because of a major initiative on qualified health claims that was introduced by the FDA in 1997, health claims were redefined under the qualified health claims standard (5). The SSA standard is a rigorous standard that requires a high level of confidence in the validity of a substance-disease relationship (5). Because of court decisions dealing with health claims for dietary supplements that raised First Amendment issues and because of a major initiative on qualified health claims that was introduced by the FDA in 1997, health claims were redefined under the qualified health claims standard (5). The SSA standard is a rigorous standard that requires a high level of confidence in the validity of a substance-disease relationship (5).
Evidence-based review of health claims

A thorough review of the scientific evidence supporting a health claim is conducted by the FDA to ascertain the level of evidence needed to support an SSA or qualified health claim. The FDA reviews studies that must be submitted in petitions seeking a specific health claim. Through a literature search, the agency identifies additional studies that are considered to be relevant to the petitioned health claim. The agency separates individual reports of human studies from other types of data and information. The FDA focuses its review on reports of human intervention and observational studies (6). Besides individual reports of human studies, the agency considers other types of data and information—e.g., meta-analyses, review articles, and animal and in vitro studies—in its review. These other types of data and information can be useful in assisting the agency in understanding the scientific issues surrounding the substance, the disease or health-related condition, or both, but cannot by themselves support a health claim relationship.

The FDA evaluates the individual reports of human studies to ascertain whether any scientific conclusions can be drawn from each study. The absence of critical factors such as a control group or appropriate statistical analysis would prevent the drawing of scientific conclusions from the study (7, 8). Studies from which the FDA cannot draw any scientific conclusions about the substance-disease relationship are eliminated from further review.

Health claims involve reducing the risk of a disease in persons who do not already have the disease that is the subject of the claim. Therefore, the FDA considers evidence from studies of persons diagnosed with the disease that is the subject of the health claim only if that evidence is scientifically appropriate to extrapolate to persons who do not have the disease.

The FDA rates the relevant human intervention and observational studies for quality (6). This quality rating is based on several criteria related to study design (e.g., whether a placebo control was or was not used), data collection (e.g., type of dietary assessment method), the quality of the statistical analysis, the type of outcome measured (e.g., disease incidence or validated surrogate endpoint), and study population characteristics other than relevance to the US population (e.g., selection bias and whether important information about the study subjects—e.g., age or smoking status—was gathered and reported).

Finally, the FDA evaluates the findings of these remaining studies. The agency then ranks the strength of the total body of publicly available evidence. The agency conducts this ranking evaluation by considering the study type (e.g., intervention, prospective cohort, case-control, or cross-sectional), the quality rating, the quantity of evidence (number of the various types of studies and sample sizes), whether the body of scientific evidence supports a substance-disease relationship for the US population or target subgroup, whether study results supporting the proposed claim have been replicated, and the overall consistency of the total body of evidence (6). On the basis of the totality of the scientific evidence, the FDA ascertains whether such evidence is credible to support the substance-disease relationship and, if so, authorizes an SSA health claim or issues a qualified health claim that reflects the level of scientific evidence.

Surrogate endpoints for age-related macular degeneration and cataracts

The FDA uses surrogate endpoints that have been identified by the National Institutes of Health and the FDA Center for Drug Evaluation and Research as validated biomarkers for predicting the risk of a disease. To date, no surrogate endpoints have been recognized for predicting the risk of AMD or cataracts. Therefore, at this time, the relationship between lutein or zeaxanthin intake and reduced risk of AMD or cataracts can be evaluated only by measuring the actual incidence of either disease.

EVALUATION OF INTERVENTION STUDIES

Twelve intervention studies attempted to evaluate the relationship between intake of lutein or zeaxanthin (or both) and the risk of AMD or cataracts (9–20). The FDA determined that, for one or more of the reasons discussed below, scientific conclusions about the relationship between lutein or zeaxanthin intake and the risk of AMD or cataracts could not be drawn from these 12 studies.

Three studies evaluated subjects who had age-related maculopathy, AMD, or cataracts (9, 17, 18). These studies evaluated the treatment effect of the intake of lutein or zeaxanthin (or both), rather than the effect of those nutrients in reducing the risk of AMD or cataracts. The FDA would consider evidence from studies in persons already diagnosed with AMD or cataracts if it is scientifically appropriate to extrapolate to persons who do not have the disease. Given that such evidence is not available, the agency could not draw any scientific conclusions from these studies.

Eight studies measured macular pigment density, which is not recognized as a surrogate endpoint for the risk of AMD or cataracts (11–12, 14–16, 19, 20). Macular pigment is an effective filter of damaging blue light, which causes retinal injury. Therefore, it has been hypothesized that increased macular pigment density may protect against AMD. Whereas a body of evidence exists for an association between macular disease and low macular pigment density, no evidence exists that high macular pigment density confers a protective effect (21). Although macular pigment density may be associated with the risk of AMD (16), other researchers have cautioned that further research is needed as to whether increasing macular pigment density has a protective effect against AMD (22).

Eight studies did not include a control group (10, 12–17, 20). Therefore, it could not be ascertained whether changes in the endpoint of interest were due to lutein or zeaxanthin intake or to unrelated and uncontrolled extraneous factors (7).

With regard to the relationship between AMD risk reduction and the intake of lutein or zeaxanthin (or both), 6 studies provided to subjects a conventional food or supplement that included nutrients other than lutein or zeaxanthin that could be responsible for any protective effect observed in the study (9, 11, 12, 15, 17, 19). With respect to intervention studies of foods and multivitamin supplements, it is not possible to determine accurately...
whether any observed effects on the risk of AMD are due to lutein or zeaxanthin (or both), interactions between lutein or zeaxanthin (or both) and other nutrients, or other nutrients acting alone or together. In 4 of these 6 studies (9, 15, 17, 19), the subjects were given a supplement that contained nutrients other than lutein or zeaxanthin (eg, vitamin C, vitamin E, and zinc) that have been suggested to have a role in protecting against retinal deterioration. Falsini et al (9) and Bartlett and Eperjesi (19) stated that some evidence suggests that vitamin C, vitamin E, and zinc may have a role in preventing AMD. In the other 2 studies (11, 12), the subjects were given spinach, which contains nutrients such as vitamins C and E, as well as lutein and zeaxanthin.

EVALUATION OF OBSERVATIONAL STUDIES

Twenty-three observational studies attempted to evaluate the relationship between lutein or zeaxanthin (or both) intake and the risk of cataracts or AMD. For the reasons discussed below, scientific conclusions could not be drawn from these 23 studies.

Fourteen observational studies estimated lutein intake by estimating the dietary intake of lutein-containing foods (23–36). In observational studies that calculate nutrient intake from conventional foods, measures of lutein intake are based on recorded dietary intake methods, such as food-frequency questionnaires, diet recalls, or diet records, in which the types and amounts of foods consumed are estimated. Lutein and zeaxanthin concentration values are then estimated by using typical lutein and zeaxanthin concentration values for the food product category, according to a source such as the US Department of Agriculture’s National Nutrient Database for Standard Reference. A common weakness of observational studies is their limited ability, because of subjects’ poor memory, subjects’ overestimation or underestimation of portion sizes, and recall bias, to ascertain the actual food or nutrient intake for the population studied (37). Furthermore, the lutein content of foods can vary because of food processing and cooking procedures (38). Thus, it is difficult to derive an accurate amount of the nutrient consumed from estimated reports of dietary intake from conventional foods.

In addition, conventional foods contain not only lutein and zeaxanthin but also other nutrients that may be associated with the metabolism of lutein or zeaxanthin or the pathogenesis of AMD or cataracts. Because foods consist of many nutrients and substances, it is difficult to study the nutrient or food components in isolation (39). For example, spinach is abundant in lutein, zeaxanthin, and β-carotene. Although cooked spinach was associated in a prospective study with a lower risk of cataract extraction (ie, the risk of developing cataracts severe enough to require extraction), neither lutein, zeaxanthin, nor β-carotene was associated with a lower risk of cataract extraction (32). Thus, it is difficult to evaluate an association of a nutrient, such as lutein or zeaxanthin, when other nutrients in foods or multinutrient supplements may have an effect on the risk of AMD or cataracts.

Nine observational studies measured blood (serum or plasma), adipose tissue, or retinal concentration of lutein or zeaxanthin (or both) as a marker of intake (22, 40–47). Observational studies have shown that dietary lutein and zeaxanthin intakes are poorly correlated with concentrations of lutein and zeaxanthin in the serum (range: \( r = 0.03–0.24 \); 45–49) or tissue (\( r = 0.06–0.25 \); 48, 49). This poor correlation can be attributed, in part, to various factors associated with lutein and zeaxanthin concentrations, including sex, race, age, smoking, alcohol consumption, serum cholesterol concentrations, and level of physical activity (50, 51). In addition, other, still unknown factors may influence the blood concentrations of lutein and zeaxanthin (50). Furthermore, serum lutein and zeaxanthin concentrations reflect intake over a short period of time and therefore may not be representative of long-term consumption (50). Because serum and tissue concentrations of lutein and zeaxanthin are poorly correlated with dietary intake, and because many known and unknown factors can alter these concentrations, no scientific conclusions about the relation between the intake of lutein or zeaxanthin and a reduction in the risk of AMD or cataracts could be drawn from these 9 studies.

CONCLUSION

In summary, the FDA determined that there were no intervention or observational studies from which scientific conclusions could be drawn about the relationship between the intake of lutein or zeaxanthin and the risk of AMD or cataracts. Therefore, the agency concluded that there was no credible evidence to support a health claim for lutein or zeaxanthin intake and the risk of AMD or cataracts (52).

REFERENCES

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