Electroretinographic Effects of Omega-3 Fatty Acid Supplementation on Dry Age-Related Macular Degeneration

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**Objectives:** To evaluate the effects of high-dose oral omega-3 fatty acid supplementation on electroretinography and omega-3 index in patients with dry age-related macular degeneration.

**Design:** Single institution, prospective, nonrandomized, noncomparative interventional case series comprising 34 eyes of 17 patients older than 50 years of age with early to intermediate age-related macular degeneration. Patients received oral supplementation with 4 g of omega-3 fatty acids daily (840 mg eicosapentaenoic acid/2520 mg docosahexaenoic acid) for 6 months. The main outcome measures included Early Treatment Diabetic Retinopathy Study best-corrected visual acuity, change in N1 and P1 peak amplitudes on multifocal electroretinographic testing, and change in serum omega-3 index.

**Results:** Mean baseline Early Treatment Diabetic Retinopathy Study best-corrected visual acuity letter score was 77 letters (Snellen equivalent of 20/32). There were no statistically significant changes in visual acuity (P = .12) or retinal function by multifocal electroretinographic testing. Serum omega-3 index increased by an average of 7.6% during the course of the study (P < .001). Study limitations included the relatively short duration of the study and small number of participants.

**Conclusions:** Short-term supplementation with high doses of omega-3 fatty acids does not result in any measurable changes in visual acuity or retinal function by multifocal electroretinographic testing. Dietary supplementation with 4 g of omega-3 fatty acids results in a significant increase in serum omega-3 index in patients with dry age-related macular degeneration and may provide a useful clinical measure for future studies.

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fatty acids in the pathophysiology of AMD is unclear. Omega-3 fatty acids are essential constituents in all tissues of the body involved primarily in cell membrane structure, but they are particularly prominent in the retina. Specifically, DHA accounts for 50% to 60% of the fatty acid content of rod photoreceptor outer segments and is thought to play an important role in the synthesis of disk membranes and other key photoreceptor processes.12-15 Animal models of age-related retinal degeneration have demonstrated a protective effect of dietary supplementation with omega-3 fatty acids that can be measured with electroretinographic (ERG) testing.16 However, to our knowledge, clinical data on this topic are limited. A meta-analysis by Chong et al10 of 9 studies reported that a high dietary intake of omega-3 fatty acids was associated with a decrease of up to 38% in the risk for late AMD. The Blue Mountain Eye Study, a cohort study, reported that a regular diet high in omega-3 polyunsaturated fat, especially from fish, seems to protect against early and late AMD.9 Similarly, a large cohort study of more than 38,000 women followed up for 10 years showed a significantly decreased incidence of AMD in those who consumed the highest amount of omega-3 fatty acids.10 Although these studies suggest a benefit from a diet rich in omega-3 fatty acids in patients with AMD, the mechanism, optimal daily intake, and ocular safety profile are unknown. As such, the current literature does not support the routine use of omega-3 fatty acid oral supplementation for patients with AMD. However, prospective studies in the cardiac literature do support the intake of between 0.5 g and 1.8 g per day for secondary prevention in patients with coronary artery disease.11 The recommended dose for patients using omega-3 supplements for triglyceride control is even higher, at 2 g to 4 g per day.12,13 Whether omega-3 fatty acid supplementation at this dosage is beneficial for AMD is unknown. In our study, we chose to use a dose of 4 g, as the published observational studies of patients with AMD suggest a dose-response relationship regarding omega-3 dietary intake.

The HS-Omega-3 Index (OmegAQuan LLC) is a blood test that measures the red blood cell membrane content of omega-3 fatty acids and is reported as a percentage of total red blood cell fatty acids identified. While this test has not yet been used in any published studies in patients with AMD, to our knowledge, it has been validated as a reliable and reproducible biomarker for serum levels of omega-3 fatty acids and has been used in a number of epidemiologic and interventional studies, particularly in the cardiac literature.18-26 Additionally, it has been validated as an independent risk factor for cardiovascular disease and sudden cardiac death, with a level of less than 4% conferring an increased risk and a level greater than 8% conferring a decreased risk.25,26 While the ideal omega-3 index in patients with AMD is unknown at this time, given the results of the cardiac data, the omega-3 index presents a novel target for therapy in AMD, as well as an important test that should likely be included in future prospective studies of oral supplementation with omega-3 fatty acids.

While ERG has been used in animal models of age-related retinal degeneration, to our knowledge, few authors have evaluated the role of ERG testing in patients with AMD.10,27 Electroretinography can provide sensitive information on retinal function and may be a useful tool in assessing retinal function in AMD.27,28 Multifocal ERG (mfERG) testing, under our current standard protocol, measures the photopic response of the central 24° of the retina and allows independent, sensitive measurements of both central and peripheral retinal function.29-32 These metrics allow for monitoring of both macular disease and the processes that may have a larger effect on the retina. Given the ubiquity of omega-3 fatty acids and their importance in photoreceptor structure and function, ERG testing provides a potential means of measuring the therapeutic effect of omega-3 supplementation, which has been demonstrated in at least 1 animal study.10 Additionally, mfERG is a particularly useful tool to measure pharmacologically induced retinal toxicity and may help identify any potential retinotoxic effects of omega-3 fatty acids.10

In the current study, we sought to determine whether oral supplementation with high doses of omega-3 fatty acids improved electroretinographic function in patients with AMD.
There were no statistically significant changes in the index between baseline and 6 months using PROC TTEST in SAS. The test was used to detect any change in the serum omega-3 index of rings from baseline using SAS PROC MIXED. The paired t test of best-corrected visual acuity and peak/needle measurement was fit for the changes in the mean of outcome variables while accounting for the above correlations through appropriate specification of the residual covariance structure. Separate models were fit for the changes of best-corrected visual acuity and peak/needle measurement of rings from baseline using SAS PROC MIXED. The paired t test was used to detect any change in the serum omega-3 index between baseline and 6 months using PROC TTEST in SAS.

### RESULTS

Thirty-four eyes of 17 patients were included in the study. All 17 patients were white, 12 were women (71%), and they had a mean age of 69 years (range, 56-89 years). Mean visual acuity (best-corrected Early Treatment Diabetic Retinopathy Study letter score, N1 and P1 peak amplitude over all 6 rings of the custom group) was considered.

Serum omega-3 index was drawn at baseline and at the end of the study. Primary outcome measures were mean changes in Early Treatment Diabetic Retinopathy Study letter score, N1 and P1 peak amplitude over all 6 rings of the custom group average on mfERG testing, and serum omega-3 index.

All statistical analyses were conducted using SAS version 9.2 (SAS Institute). Multiple measurements of the same individual were taken repeatedly, which allowed the direct study of change over time. Observations from different individuals were independent; however, repeated measurements of the same individual were not assumed to be independent. Correlations existed among repeated measurements at the 4 points, between the 2 eyes at each point, and among 6 rings within 1 study within each eye at each time. Linear mixed-effects models for longitudinal data were used to fit a linear regression model for the mean of outcome variables while accounting for the above correlations through appropriate specification of the residual covariance structure. Separate models were fit for the changes of best-corrected visual acuity and peak/needle measurement of rings from baseline using SAS PROC MIXED. The paired t test was used to detect any change in the serum omega-3 index between baseline and 6 months using PROC TTEST in SAS.

Multiple observational studies in the literature suggest a beneficial role for dietary omega-3 fatty acids in patients with AMD. The precise mechanism of this potential protective effect is unknown. Animal studies have highlighted the importance of omega-3 fatty acids in the structure of photoreceptor outer segments. Additionally, animal studies have supported a variety of retinal protective mechanisms of omega-3 fatty acids including anti-inflammatory, anti-angiogenic, anti-apoptotic, and antioxidative properties. Animal studies have demonstrated that oral supplementation with omega-3 fatty acids can protect against choroidal neovascularization following laser photoocoagulation, may reduce other forms of pathologic angiogenesis, and is protective against age-related degeneration of retinal function. Many observational and cohort studies suggest that diets high in omega-3 fatty acids are protective against AMD in humans. Currently, the Age-Related Eye Disease Study 2 is testing a dose of 1 g of omega-3 fatty acid (650 mg EPA/350 mg DHA) oral supplementation in patients with dry AMD. In our study, there were no statistically significant changes in mfERG testing with 6 months of high-dose oral omega-3 fatty acid supplementation in patients with dry AMD. This may be due in part to both the relatively short-term nature of our study in relation to the slow progression of dry AMD and the fact that our patients had only early to intermediate disease with relatively good retinal function at the onset of the study. In a recent animal study using a transgenic stargardt-like degeneration mouse model, "..."
model, a protective effect of dietary DHA was reported. Retinal function was monitored through electrophysiologic testing. However, the benefits of DHA were only seen after at least 6 months of supplementation, with a greater effect with longer supplementation. It is possible that a positive effect of EPA and DHA supplementation in vision or mfERG testing of patients with AMD may be seen with longer follow-up or in patients with more severe disease and at a higher risk for progression. Similarly, the benefits to preservation of visual acuity may become more apparent with longer follow-up. However, the lack of any significant change in mfERG amplitudes, both in the central macula and total retinal response, as well as visual acuity, does argue against any potential deleterious effect of omega-3 fatty acids on retinal function and supports the current literature that omega-3 fatty acid supplementation is safe and well tolerated.

The increase in serum omega-3 levels was highly significant. To our knowledge, this is the first study to use the HS-Omega-3 Index to measure changes in systemic levels of omega-3 fatty acids with oral supplementation in patients with AMD (determined through literature search on PubMed and in discussion with OmegaQuant LLC President and Chief Executive Officer William Harris, PhD). The increase in the omega-3 index seen in our study is an important step toward the validation of this test to measure a therapeutic response in these patients. Whether oral supplementation with omega-3 fatty acids is beneficial for patients with AMD, and at what dose, is still unknown. Though these questions are currently under investigation, the accuracy of the omega-3 index, in combination with the information obtained from it, should likely be included in future studies of omega-3 supplementation and may help to put the results of such studies into proper clinical context.

There are a number of limitations to this study. As it was an interventional case series, there was no control group with which to compare. As discussed previously, dry AMD is typically a slowly progressive disease, particularly in the early and intermediate stages, and our follow-up period of 6 months may not have been long enough to reliably detect a significant beneficial or deleterious effect of omega-3 supplementation. Our study is also limited by the relatively small number of patients studied. Additionally, interventional bias may affect patient performance, as all subjects received the study drug. Finally, although the omega-3 index has been well studied in the cardiac literature, there is currently a lack of clinical context for this test for patients with AMD.

Despite its limitations, our pilot study suggests that high-dose oral supplementation with omega-3 fatty acids is safe and well tolerated. Furthermore, given its importance in cardiac disease, the omega-3 index may play an important role for risk assessment and may provide a therapeutic target for risk reduction in patients with AMD and deserves further study. Larger, prospective, randomized studies are needed to better define the role of omega-3 fatty acid supplementation and potential dose variation in the management of dry AMD.

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Author Contributions: Dr Ho had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Conflict of Interest Disclosures: Dr Ho is a Scientific Advisory Board member for Physician Recommended Nutriceuticals, and Dr Fineman is a consultant for Physician Recommended Nutriceuticals.

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REFERENCES


