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# Dietary Intake of Omega-3 Fatty Acids From Fish and Risk of Diabetic Retinopathy

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## JAMA OPHTHALMOLOGY

### Dietary Marine $\omega$ -3 Fatty Acids and Incident Sight-Threatening Retinopathy in Middle-Aged and Older Individuals With Type 2 Diabetes: Prospective Investigation From the PREDIMED Trial

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**IMPORTANCE** Diabetic retinopathy (DR) is a devastating complication of individuals with type 2 diabetes mellitus. The retina is rich in long-chain  $\omega$ -3 polyunsaturated fatty acids (LC $\omega$ 3PUFAs), which are substrate for oxylipins with anti-inflammatory and antiangiogenic properties. Experimental models support dietary LC $\omega$ 3PUFA protection against DR, but clinical data are lacking.

**OBJECTIVE** To determine whether LC $\omega$ 3PUFA intake relates to a decreased incidence of sight-threatening DR in individuals with type 2 diabetes older than 55 years.

**DESIGN, SETTING, AND PARTICIPANTS** In late 2015, we conceived a prospective study within the randomized clinical trial Prevención con Dieta Mediterránea (PREDIMED), testing Mediterranean diets supplemented with extra virgin olive oil or nuts vs a control diet for primary cardiovascular prevention. The trial was conducted in primary health care centers in Spain. From 2003 to 2009, 3614 individuals aged 55 to 80 years with a previous diagnosis of type 2 diabetes were recruited. Full data were available for 3482 participants (48% men; mean age 67 years).

**EXPOSURES** Meeting the dietary LC $\omega$ 3PUFA recommendation of at least 500 mg/d for primary cardiovascular prevention, as assessed by a validated food-frequency questionnaire.

**MAIN OUTCOMES AND MEASURES** The main outcome was incident DR requiring laser photocoagulation, vitrectomy, and/or antiangiogenic therapy confirmed by an external adjudication committee.

**RESULTS** Of the 3482 participants, 48% were men and the mean age was 67 years. A total of 2611 participants (75%) met target LC $\omega$ 3PUFA recommendation. During a median follow-up of 6 years, we documented 69 new events. After adjusting for age, sex, intervention group, and lifestyle and clinical variables, participants meeting the LC $\omega$ 3PUFA recommendation at baseline ( $\geq$ 500 mg/d) compared with those not fulfilling this recommendation ( $<$ 500 mg/d) showed a 48% relatively reduced risk of incident sight-threatening DR, with a hazard ratio of 0.52 (95% CI, 0.31-0.88;  $P = .001$ ). This association was slightly stronger for yearly updated LC $\omega$ 3PUFA intake (relative risk, 0.48; 95% CI, 0.28-0.82;  $P = .007$ ).

**CONCLUSIONS AND RELEVANCE** In middle-aged and older individuals with type 2 diabetes, intake of at least 500 mg/d of dietary LC $\omega$ 3PUFA, easily achievable with 2 weekly servings of oily fish, is associated with a decreased risk of sight-threatening DR. Our results concur with findings from experimental models and the current model of DR pathogenesis.

**TRIAL REGISTRATION** clinicaltrials.gov Identifier: [ISRCTN35739639](https://clinicaltrials.gov/ct2/show/study?term=ISRCTN35739639)

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In the October 2016 issue of *JAMA Ophthalmology*, Sala-Vila and colleagues<sup>1</sup> reported findings from the Prevención con Dieta Mediterránea (PREDIMED) showing that among older individuals with type 2 diabetes, dietary intake of at least 500 mg/d of long-chain  $\omega$ -3 fatty acids (2 weekly servings of fish) was associated with a nearly 50% relative risk reduction for vision-threatening diabetic retinopathy, defined as requiring treatment with laser, vitrectomy, or intravitreal injections of anti-vascular endothelial growth factor (anti-VEGF) agents. PREDIMED included patients at high risk for developing cardiovascular disease randomized to receive 1 of 3 diets: a Mediterranean diet supplemented with extra-virgin olive oil, a Mediterranean diet supplemented with mixed nuts (combination of walnuts, hazelnuts, and almonds), or a low-fat

control diet.<sup>2</sup> Participants assigned to the 2 Mediterranean diets had an approximately 30% reduction in cardiovascular events (myocardial infarction, stroke, or death from cardiovascular causes) vs those in the low-fat control diet (3.4% mortality in the Mediterranean diet with nuts group, 3.4% for the Mediterranean diet supplemented with extra-virgin olive oil group, and 4.4% in the control diet group at 4.8 years).

Of the 7447 participants in PREDIMED, 3614 had type 2 diabetes at baseline. Subsequent analyses of the effect of the Mediterranean diets on the complications of diabetes demonstrated that the Mediterranean diet supplemented with extra-virgin olive oil also reduced the risk of incident treatments for vision-threatening diabetic retinopathy but not for diabetic nephropathy.<sup>3</sup>

Animal studies suggest a causal pathway for long-chain  $\omega$ -3 polyunsaturated fatty acids (LC $\omega$ 3PUFAs) found in fish for reducing the risk of diabetic retinopathy. Mouse experiments have shown that adding LC $\omega$ 3PUFAs to the diet reduces the progression of retinopathy compared with LC $\omega$ 3PUFAs controls.<sup>4,5</sup> These animal studies found that a 2% change in dietary intake of LC $\omega$ 3PUFAs ( $\omega$ -3 vs  $\omega$ -6 fatty acids) resulted in a 2-fold increase in retinal LC $\omega$ 3PUFAs, which may be the cause for the reduction in retinal nonperfusion and neovascularization.

The American Heart Association<sup>6</sup> recommends a diet that includes approximately 500 mg/d of LC $\omega$ 3PUFAs to maintain good cardiovascular health, an amount easily achieved by eating 2 servings of fish per week. Two servings of fish per week could be considered a reasonable proxy for ingesting sufficient amounts of LC $\omega$ 3PUFAs to influence diabetic retinopathy.

In PREDIMED,<sup>1</sup> intake of dietary LC $\omega$ 3PUFAs was estimated using a validated dietary questionnaire administered at baseline and annually and included consumption of any of 8 different types of seafood. Complications of diabetes (including treatments for vision-threatening diabetic retinopathy) were collected by self-report and validated by medical record review.

At baseline, among the cohort of 3482 older persons (mean age, 67.5 years) with type 2 diabetes, 2611 (75%) consumed at least 500 mg/d of LC $\omega$ 3PUFAs. During a mean follow-up of 6 years, there were 69 new vision-threatening diabetic retinopathy events requiring laser photocoagulation, vitrectomy, and intravitreal injections of anti-VEGF agents. The risk was lower among participants who had consumed the target amounts of LC $\omega$ 3PUFAs (17 cases per 9817 person-years) vs those who consumed less (52 cases per 10 587 person-years).<sup>1</sup> This finding translates into a statistically significant risk reduction for needing treatments for vision-threatening diabetic retinopathy for those who consumed 500 mg/d of LC $\omega$ 3PUFAs (adjusted hazard ratio, 0.41; 95% CI, 0.23-0.72).

This analysis from PREDIMED was an observational study within a randomized clinical trial (RCT). Thus, the observed differences in risk of diabetic retinopathy could be due to fish consumption, but also could be related to other lifestyle factors. Participants who met the LC $\omega$ 3PUFAs consumption target tended to be younger, had a higher prevalence of smoking, had a lower prevalence of hypertension or antihypertension treatment, and used less insulin, all factors that could have influenced the course of diabetic retinopathy.

Despite this limitation, studying the role of fish consumption in reducing diabetic retinopathy rates would be difficult to assess in an RCT because true random assignments may be hard to achieve in such a dietary trial. Thus, understanding this relationship will have to rely on observational data.

The benefits of LC $\omega$ 3PUFA supplements in human health are not entirely clear.<sup>4,5</sup> An RCT of oral supplementation with LC $\omega$ 3PUFAs in 12 536 persons with type 2 diabetes failed to show a beneficial effect in reducing the risk of cardiovascular disease.<sup>7</sup> Ingestion of more fish reduces the risk of having age-related macular degeneration (AMD) at baseline and of developing late AMD; however, the 4203-person Age-Related Eye Disease Study 2 (AREDS2)<sup>8</sup> failed to show a benefit in AMD development with 1 g of LC $\omega$ 3PUFAs given for 5 years in patients at high risk for developing late AMD. Early dietary studies suggested that LC $\omega$ 3PUFAs might reduce cardiovascular disease in the general population, although more recent RCTs of LC $\omega$ 3PUFA oral supplementation did not find either beneficial or harmful effects on cardiovascular disease.<sup>9</sup> Observational studies showed beneficial relationships between dietary fish and reduced risk of dementia but this finding was not apparent when RCTs of LC $\omega$ 3PUFA supplementation were performed.<sup>10</sup>

Although the assumed benefits of dietary fish intake are based on observational data, the totality of epidemiological evidence suggests that eating fish may be important for several diseases. PREDIMED was conducted in Spain and 75% of the cohort had achieved the consumption target; in contrast, only 20% of the AREDS2 cohort in the United States achieved its target. Genetic differences and other lifestyle factors may contribute to the course of diabetic retinopathy. However, analyses of diets from several different countries and continents have demonstrated a consistent protective effect of fish consumption for AMD.

Although fish ingestion might improve eye health for patients with type 2 diabetes, prevention of eye disease is not the only reason to recommend adding fish to the diet. The American Heart Association recommends eating fish twice per week to reduce cardiovascular disease risk. In addition to diets replete with fish, fruits, and vegetables, lifestyles that emphasize weight control and eliminate tobacco may play key roles in reducing cardiovascular disease. Even though the data supporting increased ingestion of fish to improve health outcomes are imperfect, this recommendation may help reduce the risk of retinopathy and cardiovascular disease, with little downside.

## ARTICLE INFORMATION

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