**Objective:** To evaluate whether a diet high in long-chain \( \omega-3 \) fatty acids can slow the rate of visual acuity loss among patients with retinitis pigmentosa receiving vitamin A palmitate.

**Methods:** We calculated dietary intake from questionnaires completed annually by 357 adult patients from 3 randomized trials who were all receiving vitamin A, 15 000 IU/d, for 4 to 6 years. Rates of visual acuity decline were compared between those with high (\( \geq 0.20 \text{ g/d} \)) vs low (\(< 0.20 \text{ g/d} \)) \( \omega-3 \) intake. Analyses took age into account.

**Results:** Mean rates of decline of acuity were slower among those with high \( \omega-3 \) intake: Early Treatment Diabetic Retinopathy Study distance acuity: high intake = 0.59 letter per year, low intake = 1.00 letter per year, \( P = .001 \); Snellen retinal acuity: high intake = 1.5% per year, low intake = 2.8% per year, \( P = .03 \).

**Conclusions:** We conclude that mean annual rates of decline in distance and retinal visual acuities in adults with retinitis pigmentosa receiving vitamin A, 15 000 IU/d, are slower over 4 to 6 years among those consuming a diet rich in \( \omega-3 \) fatty acids. To our knowledge, this is the first report that nutritional intake can modify the rate of decline of visual acuity in retinitis pigmentosa.


**METHODS**

**RETINITIS PIGMENTOSA HAS A prevalence of about 1 in 4000; about 2 million people are affected worldwide.**1-8 Patients typically report night blindness in adolescence and loss of side vision in young adulthood. As the condition advances, they develop tunnel vision and some become virtually blind by age 60 years. Ocular findings include waxy pallor of the optic discs, attenuated retinal vessels, and intraretinal pigment around the midperiphery. The majority develop central posterior subcapsular cataracts. Patients have elevated final dark adaptation thresholds and reduced and delayed electroretinograms (ERGs).9-13 Measures of visual function9-13 and histopathologic studies14,15 have established that visual loss occurs because of loss of function and degeneration of rod and cone photoreceptors across the retina.

Three clinical trials conducted by us in adults with typical retinitis pigmentosa from 1984 to 1991,16 1996 to 2001,17,18 and 2003 to 200819 provided evidence that oral vitamin A as retinyl palmitate (15 000 IU/d) alone or in combination with an \( \omega-3 \)-rich diet (\( \geq 0.20 \text{ g/d} \)), on average, slowed the rate of decline of retinal function in this condition without toxic adverse effects. In these trials of 4- to 6-year duration, treatment effects were observed on the rate of decline of the ERG16 or visual field18,19 but no significant effects on decline in distance or retinal acuity were reported.

Visual acuity declines, on average, very slowly in patients with retinitis pigmentosa.20-22 Since eligibility criteria for the 3 trials were comparable and testing methods were the same for measuring acuity and estimating dietary \( \omega-3 \) intake, we hypothesized that by combining data from all 3 clinical trials we would have sufficient statistical power to clarify whether any effect of \( \omega-3 \) intake on acuity occurred over a 4- to 6-year period.

**RESULTS**

**METHODS**

We analyzed visual acuity data from 3 clinical trials conducted by us among patients with typical retinitis pigmentosa from 1984 to 1991 (clinical trial 1), 1996 to 2001 (clinical trial 2), and 2003 to 2008 (clinical trial 3). Each had been approved by the institutional review boards of the Massachusetts Eye and Ear Infirmary and Harvard Medical School and each
had been conducted in accord with the guidelines of the Declaration of Helsinki. In each trial, informed consent had been obtained from the patients after explanation of the nature and possible consequences of the trial. We included nearly all available patients (aged 18-60 years) in these analyses. We identified 7 patients (3 from trial 1, 3 from trial 2, and 1 from trial 3) as outliers for decline in Early Treatment Diabetic Retinopathy Study (ETDRS) acuity based on the Generalized Extreme Studentized Deviate Test and excluded their data from analyses. In addition, for 9 patients who participated in 2 of the trials and 1 patient who participated in all 3 trials, data used in the present analyses were restricted to the first trial in which they participated. From trial 1, we included data from 143 of the 146 patients aged 18 to 49 years receiving vitamin A as retinyl palmitate, 15 000 IU/d, for 4 to 6 years; from trial 2 we included data from 101 of the 108 patients aged 18 to 56 years receiving this dose of vitamin A for 4 to 5 years; and from trial 3, we included data from 113 of the 121 patients aged 18 to 60 years receiving this dose of vitamin A for 4 to 5 years, for a total sample of 357 patients. In each trial, patients were screened according to comparable preset eligibility criteria. These eligibility criteria included a best-corrected Snellen distance visual acuity of 20/100 or better in at least 1 eye. In each trial, patients agreed not to know their group assignment or the course of their condition until the end of the study. Eligible patients had been reexamined 6 to 8 weeks after the screening examination before treatment and then annually thereafter during treatment. In each trial, all staff in contact with the patients had been masked to treatment group assignment and each examination had been conducted without prior information on results of previous examinations. In each trial, the data had been monitored by an independent Data and Safety Monitoring Committee selected by the National Eye Institute.

In all 3 trials, patients were evaluated under the same test conditions. They completed the Willett food frequency questionnaire at screening and at annual follow-up visits with a clinical coordinator. They then had an ophthalmic examination including a measure of ETDRS distance acuity at 3.2 m and, after dilation, Snellen retinal acuity with a Guyton-Minkowski retinal potential acuity meter, which projected a numerical acuity chart on the retina in a narrow beam that can bypass a cataract. The ETDRS chart, the standard method for measuring visual acuity in clinical trials, contained 5 letters of comparable difficulty on each line; adjacent lines differed in letter size by 0.23 log unit. A different chart was used for each eye to reduce the likelihood of memorization. The ETDRS visual acuity was scored as the total number of letters identified. A numerical chart was used for measuring retinal acuity also to minimize memorization; retinal acuities were then transformed to the natural log scale. We performed a slitlamp examination to quantify the area of posterior subcapsular cataracts, if present, with a slitlamp beam, and then a fundus examination with an ophthalmoscope.

From the responses to the food frequency questionnaire, we calculated intake of long-chain ω-3 fatty acids (primarily docosahexaenoic acid), total energy intake, and other nutrients, as described elsewhere. The validity of long-chain ω-3 fatty acid intake calculated from this questionnaire has been documented by comparison with levels in adipose tissue. In trial 2, the validity of this questionnaire for estimating ω-3 intake was confirmed by the moderate correlation between dietary ω-3 intake and red blood cell phosphatidylethanolamine docosahexaenoic acid levels (r=0.53, P<.01). A level of red blood cell phosphatidylethanolamine docosahexaenoic acid of 5% or more of total red blood cell phosphatidylethanolamine fatty acids corresponded to an estimated dietary ω-3 intake of 0.20 g/d or more. Using the food frequency questionnaire, we estimated ω-3 intake for each patient by averaging the data from all examinations to minimize measurement error. Using these values, the entire study population (n = 357) was divided into those with high (≥0.20 g/d, n = 215) or low (<0.20 g/d, n = 142) ω-3 intake. The value of 0.20 g/d represents the median intake observed during the course of trial 2. Furthermore, in trial 2, patients with 0.20 g/d or more of ω-3 intake were found to have a slower loss of visual field than those with ω-3 intake less than 0.20 g/d.

Eyes with a Snellen distance acuity less than 20/100 at baseline were excluded from analysis of ETDRS or potential acuity meter data to reduce the likelihood of a floor effect. If patients became pseudophakic (n=6), or if ETDRS acuity declined to 0 letters (n=8) (comparable to ≤20/300), data from these eyes at subsequent visits were censored to eliminate any effect of cataract surgery on acuity or any possible floor effect. Visual acuity testing at 1 m was not performed. Longitudinal regression analyses were performed to compare rates of decline in distance acuity and retinal acuity by high (≥0.20 g/d) vs low (<0.20 g/d) ω-3 intake. Since there were significant differences in baseline visual acuity among these clinical trials, we included indicator variables for trial in the models used for analyses. Since Goldmann field tests were performed in trial 1 and Humphrey field tests in trials 2 and 3, we could not combine data from the 3 trials for field analyses. With respect to full-field cone ERGs, among the 375 patients receiving vitamin A, 10 participated in more than 1 trial and data from the first trial only were included. In addition, 99 patients had initial values less than 0.68 µV and could not be followed up because of a floor effect, which would be expected to occur when they reached 0.34 µV. Thus, the sample for ERG analysis included 266 patients with pretreatment amplitudes of 0.68 µV or more and analysis of the combined data was performed; the annual rate of decline of 163 patients with high ω-3 intake was compared with the rate of decline of 103 patients with low ω-3 intake.

The Table shows baseline demographic and ocular findings for the study population divided into those above and below the median intake of 0.20 g/d of ω-3 fatty acids averaged over all visits derived from the food frequency questionnaire. All patients were receiving vitamin A palmitate, 15 000 IU/d, and no significant differences were seen among those with high vs those with low dietary ω-3 intake. No significant differences were seen in any of the parameters noted in the Table beyond age and the anticipated difference in ω-3 intake.

The mean annual rates of change of distance and retinal acuity were slower among those with high ω-3 intake (≥0.20 g/d) than among those with low intake (<0.20 g/d). The mean rates of change in distance acuity were –0.59 letter per year (high ω-3 intake) vs –1.00 letter per year (low ω-3 intake) (P=.001). For retinal acuity, mean rates of change were –0.015 log unit (1.5% decline) per year for high intake vs –0.028 log unit (2.8% decline) per year for low intake (P=.03). In separate analyses, there was no significant effect of age on rate of vi-
Table. Baseline Patient Characteristics of Study Population With Retinitis Pigmentosa

<table>
<thead>
<tr>
<th>Variable</th>
<th>High (≥0.20 g/d) (n = 215)</th>
<th>Low (&lt;0.20 g/d) (n = 142)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y, mean (SE)</td>
<td>36.22 (0.69)</td>
<td>33.55 (0.76)</td>
<td>.01</td>
</tr>
<tr>
<td>Age by decade, y</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18-29</td>
<td>64 (30)</td>
<td>43 (30)</td>
<td>.01</td>
</tr>
<tr>
<td>30-39</td>
<td>64 (30)</td>
<td>65 (46)</td>
<td></td>
</tr>
<tr>
<td>40-49</td>
<td>65 (30)</td>
<td>30 (21)</td>
<td></td>
</tr>
<tr>
<td>≥50</td>
<td>22 (10)</td>
<td>4 (3)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>118 (55)</td>
<td>85 (60)</td>
<td>.41</td>
</tr>
<tr>
<td>BMI, mean (SE)</td>
<td>25.83 (0.28)</td>
<td>25.69 (0.33)</td>
<td>.77</td>
</tr>
<tr>
<td>Genetic type</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dominant</td>
<td>54 (25)</td>
<td>40 (28)</td>
<td>.66</td>
</tr>
<tr>
<td>Recessive</td>
<td>35 (16)</td>
<td>17 (12)</td>
<td></td>
</tr>
<tr>
<td>X-linked</td>
<td>15 (7)</td>
<td>14 (10)</td>
<td></td>
</tr>
<tr>
<td>Isolate</td>
<td>103 (48)</td>
<td>65 (46)</td>
<td></td>
</tr>
<tr>
<td>Undetermined</td>
<td>8 (4)</td>
<td>6 (4)</td>
<td></td>
</tr>
<tr>
<td>Dietary intake</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ω-3 Fatty acids, g/d, mean (SE)</td>
<td>0.30 (0.02)</td>
<td>0.12 (0.01)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Calories/d, mean (SE)</td>
<td>2097 (43)</td>
<td>2106 (58)</td>
<td>.89</td>
</tr>
<tr>
<td>Vitamin A, IU/d, mean (SE)</td>
<td>2346 (127)</td>
<td>2534 (161)</td>
<td>.35</td>
</tr>
<tr>
<td>Serum retinol, µg/d, mean (SE)</td>
<td>51.71 (0.71)</td>
<td>51.86 (1.04)</td>
<td>.90</td>
</tr>
<tr>
<td>Ocular findings</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Log(e) unit 1-20 retina acuity, ω-3 Intake</td>
<td>0.44 (0.02)</td>
<td>0.40 (0.02)</td>
<td>.20</td>
</tr>
<tr>
<td>Distance acuity, mean (SE)</td>
<td>48.98 (0.69)</td>
<td>50.20 (0.72)</td>
<td>.22</td>
</tr>
<tr>
<td>Cataract present</td>
<td>120 (56)</td>
<td>80 (57)</td>
<td>.99</td>
</tr>
<tr>
<td>Total lens area</td>
<td></td>
<td></td>
<td>.32</td>
</tr>
<tr>
<td>0 (no cataract)</td>
<td>94 (44)</td>
<td>61 (43)</td>
<td></td>
</tr>
<tr>
<td>≤1%</td>
<td>73 (34)</td>
<td>58 (41)</td>
<td></td>
</tr>
<tr>
<td>&gt;1% to ≤3%</td>
<td>33 (15)</td>
<td>17 (12)</td>
<td></td>
</tr>
<tr>
<td>&gt;3% to ≤7%</td>
<td>10 (5)</td>
<td>4 (3)</td>
<td></td>
</tr>
<tr>
<td>&gt;7% to ≤11%</td>
<td>4 (2)</td>
<td>1 (1)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviation: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared).

a P value based on t test for continuous variables and χ² test for categorical variables.

b P value based on Mantel-Haenszel χ² (test for trend).
c Values of 0.44 and 0.40 correspond to Snellen fractions of 20/31 and 20/30.
d Snellen equivalents: 48.98 letters = 20/33; 50.20 letters = 20/31.
e Among those not pseudophakic in at least 1 eye at baseline, sample sizes are 206 for high ω-3 intake and 138 for low ω-3 intake.
f Cataract area as percentage of total lens area among patients not pseudophakic in at least 1 eye at baseline.

sural acuity decline for either distance or retinal acuity (data not shown).

Figure 1 shows mean log unit annual rates of decline of visual acuity by ω-3 intake for both distance and retinal acuity. Sample sizes were 337 for distance acuity and 342 for retinal acuity. The latter sample excluded patients with pseudophakia at baseline because potential media obstruction would not be relevant in following up these patients. In Figure 1 and Figure 2, values for distance (ETDRS) acuity were obtained by multiplying the number of letters identified by 0.046 (ie, 0.02 log₁₀ unit per letter × 2.303 log unit per log₁₀ unit) so that the slopes for distance and retinal acuity were on the same (log, unit) scale.

Figure 2 shows mean log unit annual rates of visual acuity decline by quartile of ω-3 intake. Quartiles 1 and 2 combined (low ω-3 intake) had a faster rate of decline than quartiles 3 and 4 combined (high ω-3 intake) for both distance acuity (P = .003) and retinal acuity (P = .04), supporting the division of this population into those with intake of 0.20 g/d and more and those with intake less than 0.20 g/d.
Only slight changes in cataract frequency and cataract size were observed in both groups over the course of these trials. The frequency of cataract increased by 11% among those with high \( \omega-3 \) intake and by 10% among those with \( \omega-3 \) intake over 4 to 6 years. Among patients with cataracts, average cataract diameter increased by 0.07 mm over the course of these trials among those with \( \omega-3 \) intake of 0.20 g/d or more, while cataract diameter increased by 0.14 mm for those with \( \omega-3 \) intake less than 0.20 g/d. These increases were not significantly different by \( \omega-3 \) intake group. The annual rate of decline of remaining cone ERG amplitude for those with high \( \omega-3 \) intake was 9.8% and for those with low \( \omega-3 \) intake was 9.6%; the difference in rates of decline was not significant.

In this cohort of 357 patients with typical retinitis pigmentosa receiving 15 000 IU/d of vitamin A as retinyl palmitate for 4 to 6 years, those with a diet high in long-chain \( \omega-3 \) fatty acids (\( \geq 0.20 \) g/d) had a 40% slower mean annual rate of decline in distance visual acuity than those with a diet low in these fatty acids. The groups defined by high and low dietary \( \omega-3 \) intake were balanced with respect to other dietary factors and anthropometric variables except for age differences, which were controlled for in the statistical analyses. Both groups showed comparable change in posterior subcapsular cataract diameter, further suggesting that this effect of \( \omega-3 \) intake on distance acuity was not due to cataract enlargement in these patients. Since vitamin A plus an \( \omega-3 \)-rich diet slowed the rate of decline of distance and retinal acuity by about the same extent, we conclude that the benefit of this combination was due to an effect on preserving central retinal function.

Although annual rates of decline in distance and retinal acuities were significantly different when comparing patients with high vs low \( \omega-3 \) intake (\( P = .001 \) and \( P = .03 \), respectively), we could not detect a significant difference in annual rates of decline for full-field cone ERGs. Since the full-field cone ERG is generated predominantly by mid-peripheral and far peripheral cones and since no effect of \( \omega-3 \) intake could be detected in this measure, this observation suggests that the benefit of \( \omega-3 \) intake is limited to acuity and central field preservation (see below).

The mean rate of decline in letters per year on ETDRS testing was 0.59 letter for patients receiving vitamin A with high \( \omega-3 \) intake vs 1.00 letter for patients receiving vitamin A with low \( \omega-3 \) intake over a 4- to 6-year duration. If these rates are sustained over the long-term, we estimate that a representative patient who starts receiving vitamin A by age 35 years and eats an \( \omega-3 \)-rich diet (ie, one to two 3-oz servings of oily fish per week) with an ETDRS acuity of 50 letters (equivalent to 20/30 on the Snellen chart) would, on average, be expected to decline to an ETDRS acuity of 24 letters (equivalent to 20/100 on the Snellen chart) at age 79 years, whereas this patient receiving vitamin A with a low dietary \( \omega-3 \) intake (eg, less than one 3-oz serving of oily fish per week) would decline to this level at age 61 years.

We have previously reported an effect of dietary \( \omega-3 \) intake on retinal thickness as measured with the Humphrey Field Analyzer 30-2 program (size V white test light).\(^1\)\(^8\) Patients receiving vitamin A palmitate, 15 000 IU/d, with \( \omega-3 \) intake of at least 0.20 g/d had almost a 50% slower rate of decline in central visual field sensitivity as measured by the Humphrey Field Analyzer 30-2 program than those receiving this dose of vitamin A with lower \( \omega-3 \) intake (\( P = .02 \)). We concluded that for the average patient in trial 2 (aged 37 years with 869 dB of field sensitivity at baseline) intake of 0.20 g/d or more of dietary \( \omega-3 \) would result in an additional 19 years of central visual field preservation.\(^1\)\(^8\) In the present study, we find virtually the same benefit for visual acuity preservation (ie, 18 years of additional vision). Therefore, the treatment regimen of vitamin A combined with an \( \omega-3 \)-rich diet (\( \geq 0.20 \) g/d) should make it possible for many patients with typical retinitis pigmentosa to retain both visual acuity and central visual field for most of their lives.

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REFERENCES


Ophthalmic Images

Late Migration of Dexamethasone Implant Into Anterior Chamber

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Kishan Govind, BA
Shree K. Kurup, MD

A woman with pseudophakia (stable, well centered) and a history of vitrectomy received a dexamethasone implant for central retinal vein occlusion. A month later, the implant migrated into the anterior chamber. Worsening preexisting corneal edema mandated removal of the friable implant through a paracentesis.