

# Epithelial Healing and Visual Outcomes of Patients Using Omega-3 Oral Nutritional Supplements Before and After Photorefractive Keratectomy: A Pilot Study

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**Purpose:** To investigate the effect of omega-3 oral nutritional supplementation on corneal reepithelialization, visual acuity, and tear stability after photorefractive keratectomy (PRK).

**Methods:** This is a prospective, randomized, single-blinded controlled therapeutic trial using omega-3 oral nutritional supplements (TheraTears Nutrition for Dry Eyes; Advanced Vision Research—Akorn, Ann Arbor, MI) conducted at our center. Eighteen healthy patients with refractive error between  $-1$  and  $-8$  diopters were recruited and had bilateral PRK. The treatment group ( $n = 9$  subjects) received omega-3 2 weeks before surgery through 1 month after PRK. The control group ( $n = 9$  subjects) was not given omega-3. Epithelial defects were photographed on postoperative days 0 to 5. Reepithelialization (area in square millimeters) was assessed by fluorescein staining until healing. Tear breakup time (TBUT) and uncorrected distance visual acuity were measured at 1 week, and 1 and 3 months postoperatively.

**Results:** Epithelial defect in the treatment group eyes healed faster compared with that of the controls ( $P = 0.04$ ). The treatment group eyes healed at an average rate of 1.19% [SD = 0.002; 95% confidence interval (CI), 1.04%–1.34%] per hour, versus 0.83% (SD = 0.0008; 95% CI, 0.77%–0.89%) for controls (Mann–Whitney rank-sum test,  $P < 0.001$ ). The treatment group eyes maintained a significantly longer TBUT from week 1 through 3 months (mean = 9.52 seconds, SD = 0.81; 95% CI, 8.93–10.10), compared with the controls (mean = 5.52 seconds, SD = 0.81; 95% CI, 4.93–6.10;  $P < 0.001$ ), and all reached 20/20 vision versus only 4 in the control group 1 month after surgery ( $P = 0.03$ ).

**Conclusions:** Omega-3 oral nutritional supplements decreased the average time for epithelial healing, and improved TBUT and visual acuity recovery in PRK. These findings suggested that omega-3 oral nutritional supplementation may be a beneficial adjunct therapy for PRK patients.

**Key Words:** omega-3, fatty acids, PRK, cornea, tear breakup time (*Cornea* 2013;32:761–765)

Photorefractive keratectomy (PRK) is a common refractive procedure that presents minimal risk, but the risk for an inflammatory response is more significant than in laser in situ keratomileusis surgery. Local inflammation after PRK increases discomfort and healing time. Wilson<sup>1</sup> demonstrated that proinflammatory cytokines produced in response to the epithelial insult penetrate into the stroma, where they stimulate inflammatory factors. Such a response may induce pain, which can be prolonged by a more difficult healing process.<sup>1–3</sup>

An antiinflammatory regimen in PRK may speed normal epithelial healing and visual acuity recovery and minimize pain.<sup>4</sup> During surgery, ophthalmologists typically prescribe multiple antiinflammatory agents to treat postoperative inflammation. These medications control the release of proinflammatory cytokines, which would otherwise impede the healing process.

Although efficacy is the key determinant in all drug selection, safety plays an important role as well. Omega-3 essential fatty acids (EFAs) are among the most effective and safest natural antiinflammatory agents available.<sup>5,6</sup> They have already been used in the field of ophthalmology for the treatment of dry eyes and other ocular surface diseases,<sup>6,7</sup> but not for the treatment of epithelial defect after PRK. Previous studies have suggested that omega-3 EFAs can reduce the expression of conjunctival inflammatory markers,<sup>4</sup> and may have a positive effect on tear production and tear volume without affecting the meibum lipid composition or the aqueous evaporation rate.<sup>8</sup>

This study examines the effect of omega-3 oral nutritional supplementation on corneal reepithelialization as the primary outcome after PRK. Additionally, tear film restabilization and visual acuity recovery after PRK were measured as secondary outcomes.

## MATERIALS AND METHODS

The institutional review board (Human Research Protection Program) at the University of California, San Diego, reviewed and approved the study protocol. All patients signed

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the informed consent after receiving a detailed description of the PRK procedure. The eligibility criteria included age 18 years or older, refractive error between  $-1$  and  $-8$  diopters, and normal ocular examination. Pregnant or nursing mothers, and patients with any history of allergy to fish and fish products, including omega-3, were excluded.

### Regimen: Omega-3 Oral Nutritional Supplementation

This prospective, randomized, single-blinded, controlled, therapeutic trial ( $n = 36$  eyes) examines the effect of omega-3 oral nutritional supplementation on the eyes of patients after PRK. Patients from the treatment group ( $n = 9$  subjects, 18 eyes) were given omega-3 oral nutritional supplements, 1 capsule 3 times a day for 2 weeks before surgery through 1 month postoperatively along with the standard postop medications. The omega-3 oral nutritional supplements (TheraTears Nutrition for Dry Eyes, Advanced Vision Research—Akorn, Ann Arbor, MI) were equivalent to 750 mg of omega-3 EFAs both eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), 1000 mg of flaxseed oil, and about 183 IU of vitamin E per day. The control group ( $n = 9$  subjects, 18 eyes) were not given omega-3 oral nutritional supplements, but received the same medical regimen as our normal refractive patients. All patients were followed-up for at least 6 months.

### PRK Procedure

PRK was performed by the same surgeon (D.J.S) under sterile conditions as previously described.<sup>9–11</sup> The surgical field was prepared using a tetracaine and naphazoline solution (1 drop of each in the surgical eye). Plastic sterile drapes were placed, and a lid speculum and Tegaderm were inserted to expose the operative field. Topical proparacaine hydrochloride (2 drops; Bausch & Lomb, Tampa, FL) was placed into the surgical eye, and an 8-mm PRK well was placed on the center top of the cornea and filled with 20% ethanol for 20 seconds. The alcohol was swabbed with a Weck-Cel sponge and the surface was copiously irrigated with balanced saline solution. The epithelium was removed by mechanical debridement with an epithelial hoe. The same area of epithelium was removed for all cases (8-mm zone). Laser ablations were performed over the central surface using a Visx S4 (Visx, Abbott Laboratories Inc, Abbott Park, IL) or WaveLight Allegretto (Alcon Laboratories Inc, Fort Worth, TX) excimer laser and a standard or a customized laser ablation pattern. The ablated area was then rinsed with balanced saline solution. At the end of the procedure, 1 to 2 drops of steroids (Pred Forte; Allergan, Irvine, CA) and antibiotics (Zymaxid; Allergan) were applied. Slit-lamp examination, placement of fluorescein dye, and photography of the epithelial defect were then performed. A bandage contact lens (Acuvue Oasys; Vistakon, Jacksonville, FL) was placed and remained until total reepithelialization occurred.<sup>11</sup> Postoperative treatment included 0.5% ketorolac tromethamine drops (Acuvail), fluorometholone (0.25% FML Forte drops; Allergan), and 0.3% gatifloxacin drops (Zymaxid; Allergan).<sup>10</sup>

### Primary Outcome: Corneal Healing After PRK Surgery

The previously placed contact bandage lens was carefully slid to the outer limbal area of the cornea before staining (on surgery day, dye was placed directly on the corneal surface). Next, instillation of the fluorescein dye (Fluoresoft-0.35%; Holles Laboratories, Inc., Cohasset, MA) was performed and photographs were taken to capture the area of the epithelial defect. The epithelial defect could then be observed and measured until the epithelial cells were completely restored (100% reepithelialization). The bandage contact lens was removed once the epithelium was entirely healed. Each corneal defect was measured on the day of surgery and postoperatively days 1 to 6 depending on the healing process. Calculations of the area (square millimeters) of the corneal defect were performed on the basis of fluorescein staining and photographs using the Adobe Photoshop method of analysis.<sup>12</sup>

### Secondary Outcomes: Tear Film Stabilization and Visual Acuity Recovery

The same clinician measured the tear breakup time (TBUT) by instilling fluorescein dye in the inferior temporal fornix. The patient was asked to blink several times to distribute the fluorescein evenly on the corneal surface and then to stare directly ahead without blinking. The tear film was examined with a cobalt blue light from the slit lamp. A stopwatch was used to measure the interval between the last complete blink and the first appearance of a dry spot. TBUT was measured 3 times in succession for each eye. TBUT was measured on week 1, and 1 and 3 months postoperatively. Visual acuity was measured on days 1 to 6; 1 week; 1, 3, and 6 months postoperatively using the Snellen chart and was converted to logarithm of the minimum angle of resolution (logMAR) values ( $\log\text{MAR} = -\log 1/\text{Snellen visual acuity}$ ).

### Statistical Analysis

Epithelial healing, TBUT, and visual acuity were compared between the treatment and the control groups. All statistical analyses were performed using Statistica for Windows, version 9.1 (Statsoft, Tulsa, OK).<sup>13</sup> Level of statistical significance was set at  $\alpha = 0.05$ . Patients' demographic and health characteristics and ocular outcome measurements were compared between the treatment and the control groups. Background characteristics were assessed as potential confounding variables (Table 1). Continuous variables were compared using 2-sample *t* tests or Wilcoxon rank-sum tests if normality and homogeneity of variance assumptions were not met. Discrete variables were compared using  $\chi^2$  and Fisher exact tests. If differences between groups were detected and factors were found to be associated with the outcome variables, confounders were included as covariates in an analysis of covariance model.

We examined the effects of omega-3 oral nutritional supplementation on corneal reepithelialization, TBUT, and visual acuity. Corneal reepithelialization was the primary outcome. It was assessed by comparing the rate of healing of

**TABLE 1.** Descriptive Characteristics

	Omega-3-Supplemented Group (n = 9)	Control Group (n = 9)	P
Background characteristics			
Mean age in yr (SD)	31.11 (6.2)	32.11 (10.6)	0.960*
Female, n (%)	8 (88.9)	4 (44.4)	0.131†
College education, n (%)	9 (100)	8 (88.9)	1.00†
Marital status (married), n (%)	5 (55.6)	6 (66.7)	1.00†
Smoking (No.), n (%)	8 (88.9)	7 (77.8)	1.00†
Preoperative clinical characteristics			
Myopia in diopters, mean (SD); range	-3.76 (1.90); -1.25 to -8	-3.75 (1.83); -1.5 to -7.5	1.00*
Astigmatism in cylinder diopters, mean (SD); range	0.80 (0.65); 0.25 to 2.5	0.68 (0.51); 0 to 1.75	0.931*
Oblique, n (%)	6 (66.7)	2 (22.2)	
TBUT, mean (SD)	9.33 (2)	10 (0)	0.730*
Visual acuity in logMAR, mean (SD)	1.35 (.53)	1.29 (0.63)	0.856*

\*Mann-Whitney rank-sum test.  
†Fisher exact test.

the corneal epithelial defect marked by fluorescein stain between the treatment and control groups. Rate of healing was measured in percent of area healed per hour from day 0 to day 6. Area healed was measured in pixels with the Adobe Photoshop method.<sup>12</sup> Secondary outcome measures were change in TBUT, measured in seconds, and visual acuity, measured in logMAR.

A general linear model was applied on each outcome measure to allow for inclusion of covariates. If no significant covariate was found, repeated measures analyses of variance were performed on outcome measures with 1 within-subjects factor, time in days until healing for rate of healing, or time (1 week, 1 and 3 months) for TBUT and visual acuity, and 1 between-subjects factor, group (2 levels: study group receiving omega-3 oral nutritional supplementation, control group without omega-3). Time-group interaction was used to compare slopes or change in outcome scores between the treatment and control groups. When a significant interaction was identified, linear contrasts were used to compare change over time within and between the 2 groups. If assumptions of normality and homogeneity of variances were not met for each variable, a nonparametric test, that is, Mann-Whitney rank-sum test, was performed on the difference in outcome from Day 0 to follow-up reassessment. Dichotomous outcome, that is, healed versus nonhealed, was compared between the 2 groups using descriptive odds ratio. With only 9 observations per group, the effect size needed for a power of 80% was 1.4 in the rate of healing per hour, for  $\alpha = 0.05$ .

## RESULTS

### Background Characteristics

The omega-3 and control groups of patients (n = 18; mean age = 31.6 years, SD = 8.47; 66.7% women; 94.7% college graduate; 84.2% nonsmoker) were similar in background characteristics ( $P \geq 0.131$ ). All patients had bilateral PRK surgery. Outcomes from both eyes were significantly correlated at all time points,  $\rho(18) \geq 0.728$  ( $P < 0.001$ ); therefore, only the right eye was considered. Preop-

erative clinical characteristics were similar in both groups ( $P \geq 0.153$ ), including TBUT ( $P = 0.730$ ) and visual acuity in logMAR ( $P \geq 0.856$ ; Table 1). None of the potential confounders were associated with any of the outcome measures ( $P \geq 0.164$ ). Both groups were similar in postoperative residual refractive error ( $P \geq 0.394$ ), with 8 of the 9 omega-3-treated patients being plano compared with 5 of the 9 controls ( $P = 0.29$ ).

### Effects of Omega-3 Oral Nutritional Supplementation

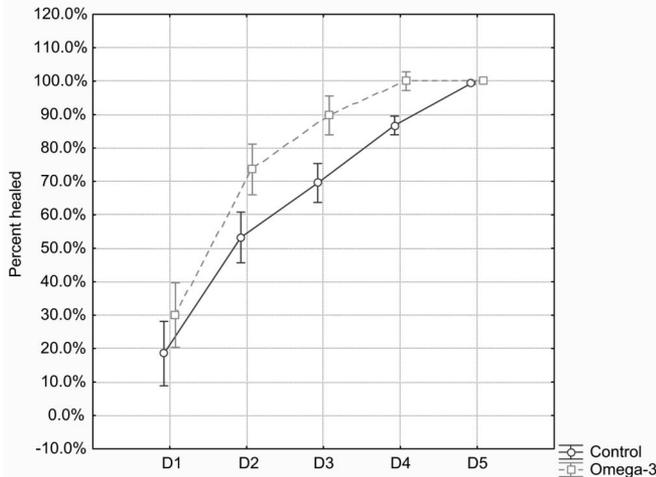
#### Primary Outcome: Corneal Reepithelialization

The rate of healing of the corneal epithelial defect measured in percent of area healed (in pixels) from day 0 to day 6 was the primary outcome of interest (Fig. 1). We measured epithelial defect until 100% of the epithelial surface was healed for both treatment and control groups. Figure 1 shows that the treatment group healed faster ( $P = 0.041$ ), with significant differences from day 3 to day 4, compared with the control group ( $P \leq 0.049$ ; Fig. 1). The treatment group healed on average at a rate of 1.19% [SD = 0.002; 95% confidence interval (CI), 1.04%–1.34%] per hour until 100% confluency, compared with 0.83% (SD = 0.0008; 95% CI, 0.77%–0.89%) per hour for the controls ( $P < 0.001$ ). The difference corresponded to an effect size of 3.75 SD and 100% power.

By day 3, 6 patients given omega-3 oral nutritional supplements were healed compared with 1 control patient ( $P = 0.05$ ). By day 4, the treatment group eyes were all healed compared with 3 of the 9 control group eyes ( $P < 0.01$ ).

#### Secondary Outcomes

Figure 2 shows that visual acuity recovery measured in logMAR was already at the 20/20 level 1 month after surgery for all patients given omega-3 oral nutritional supplements, compared with only 4 in the control group ( $P = 0.029$ ), which reached 20/25 only after 3 months. Figure 3 shows that, on average, omega-3-treated eyes maintained a significantly longer TBUT (mean = 9.52 seconds, SD = 0.81; 95% CI,



**FIGURE 1.** Effects of omega-3 oral nutritional supplements on corneal reepithelialization measured in percent healed from days 1 to 6.

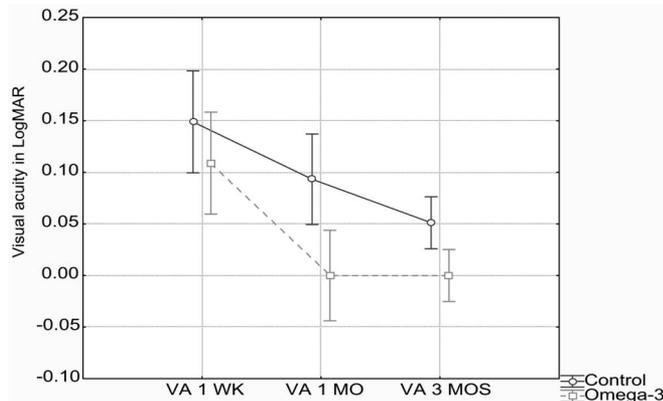
8.93–10.10), compared with the control group eyes (mean = 5.52 seconds, SD = 0.81; 95% CI, 4.93–6.10;  $P < 0.001$ ).

**DISCUSSION**

Our findings showed that corneal reepithelialization was significantly faster in patients receiving omega-3 oral nutritional supplements than for controls. This result was associated with longer TBUT and faster recovery in visual acuity.

Given the stronger insult to the epithelium and secondarily to the underlying corneal stroma in PRK, rapid reepithelialization of the cornea is key toward minimizing the risk of infection and pain.<sup>1-4,14</sup> Both oral steroid and topical steroid/nonsteroidal antiinflammatory drug regimens are usually prescribed.<sup>4</sup> Administration of steroids entails some risks such as increased intraocular pressure without careful monitoring.<sup>4</sup>

Omega-3 EFAs are essential unsaturated fatty acids and a natural antiinflammatory agent that can be found in certain fish oils and flaxseed oil.<sup>15</sup> The main differences between fish

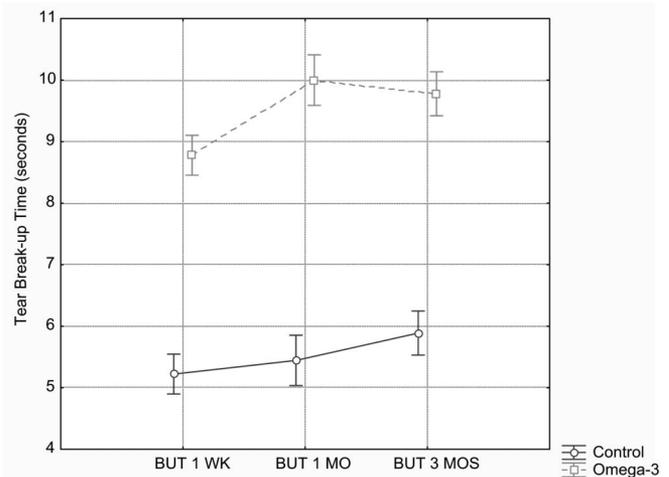


**FIGURE 2.** Effects of omega-3 oral nutritional supplements on visual acuity.

oil and vegetal sources of omega-3 EFAs such as flaxseed oil reside in their antiinflammatory components and metabolism: whereas fish oil contains EPA and DHA, both of which contribute directly to the antiinflammatory response, flaxseed oil contains alpha-linolenic acid omega-3 (57%), linoleic acid omega-6 (15%), and oleic acid omega-9 (18%). Alpha-linolenic acid must first be metabolized into EPA to enter the antiinflammatory cascade. Therefore, fish oil might have a more rapid and a larger antiinflammatory effect than flaxseed oil alone.<sup>16</sup> In this study, patients received a combination of fish and flaxseed oils. Intake of both oils as dietary supplements may be ideal as they may work synergistically to fight inflammatory agents, such as those that are present after PRK. However, this hypothesis needs to be further tested.

Despite its beneficial effect on the immune system (EPA and DHA are involved in immune function), omega-3 EFAs are lacking in our Western diet.<sup>15</sup> Omega-3 EFAs modulate prostaglandin metabolism toward antiinflammatory prostaglandin synthesis. As a result, omega-3 EFAs suppress the production of interleukin-1 beta (IL-1 $\beta$ ) by suppressing the IL-1 $\beta$  messenger RNA and the expression of cyclooxygenase 2 messenger RNA that is induced by IL-1 $\beta$ .<sup>16</sup> Previous studies suggested that omega-3 oral nutritional supplements reduced inflammation in dry eyes and ocular surface diseases.<sup>7,8</sup> Our finding that by day 4 after PRK surgery, 100% of the supplemented treatment group eyes were healed compared with only 33% of the nonsupplemented control group eyes may promote the use of omega-3 EFAs as antiinflammatory agents in PRK surgery.

Other studies have shown that the use of additional omega-3 EFAs may be beneficial in tear stabilization and may prevent inflammatory reactions to block the meibomian gland ducts and meibum stagnation.<sup>16</sup> An unstable tear film may result from abnormal meibomian gland secretions, which can lead to faster evaporation of the tear film. Supplementing the diet with high amounts of omega-3 EFAs is likely to modify the EFA composition and consequently improve the properties of the meibomian gland secretions and stabilize the



**FIGURE 3.** Effect of omega-3 oral nutritional supplements on TBUT.

tear film.<sup>16</sup> In our study, the treatment group eyes maintained a significantly longer TBUT over a 3-month period than the control group eyes.

Foster<sup>17</sup> demonstrated that one of the components of aqueous tears is the epidermal growth factor shown to be responsible for maintaining the normal ocular surface health and, most importantly, promoting wound healing. Our findings suggest that omega-3 oral nutritional supplements promoted surface healing, thereby restoring visual acuity faster. The treatment eye group reached almost 20/20 vision at 1 month postoperatively, whereas the control group eyes were still at 20/25 after 3 months.

This study had several limitations. First, a few risks are associated even with low doses of omega-3 EFA use, which include blood thinning and gastrointestinal discomfort.<sup>16</sup> Second, the number of patients was relatively small because of the extensive follow-up examinations required for this study. The difference in the rate of healing between the 2 groups was highly significant and achieved 100% power. Third, we chose not to give the omega-3 oral nutritional supplements for >2 weeks before the surgery because once refractive patients were committed to having an elective refractive surgery, they were eager to schedule their procedure. In future studies with larger samples, prolonged pretreatment with omega-3 oral nutritional supplements may prove to be even more beneficial. Fourth, this study was only single blinded: because a placebo regimen was not available, subjects were aware of their group assignment. Unlike healing and TBUT, which are objective physiological measures, visual acuity might have been affected by this bias. Fifth, in the complex cascading sequence of events involved in corneal wound healing after PRK, it is difficult to pinpoint the specific mechanism by which omega-3 EFAs might contribute to the healing process. We alluded earlier to some potential mechanisms of action, but in the absence of objective physiological markers measured in this study, we concur with Macsai's<sup>16</sup> proposed hypothesis that omega-3 EFA supplementation may improve the composition of the tear film. Our results are consistent with previous studies on dry eyes<sup>7,8</sup> and extend the scope of omega-3 EFAs to PRK surgery.

To our knowledge, this is the first therapeutic trial in PRK surgery assessing epithelial wound healing in the eyes of patients taking omega-3 oral nutritional supplements compared with the control group eyes. The addition of the omega-3 oral nutritional supplements before and after PRK

surgery decreased the average time for corneal epithelial healing and improved both TBUT and visual acuity recovery. These findings suggested that omega-3 oral nutritional supplementation may be a beneficial adjunct therapy for PRK patients.

## REFERENCES

1. Wilson SE. Everett Kinsey Lecture. Keratocyte apoptosis in refractive surgery. *CLAO J*. 1998;24:181–185.
2. Netto MV, Mohan RR, Ambrósio R Jr, et al. Wound healing in the cornea: a review of refractive surgery complications and new prospects for therapy. *Cornea*. 2005;24:509–522.
3. Ramirez-Florez S, Maurice DM. Inflammatory cells, refractive regression, and haze after excimer laser PRK. *J Refract Surg*. 1996;12:370–381.
4. McDonald MB. Role of anti-inflammatory medication: PRK. Loteprednol Etabonate Technical Paper. Part 1: Refractive. 2009;October:1–4.
5. Maroon JC, Bost JW, Borden MK, et al. Natural antiinflammatory agents for pain relief in athletes. *Neurosurg Focus*. 2006;21:4.
6. Gilbard JP. Dry eye. Natural history, diagnosis and treatment. Available at: <http://www.dryeyeinfo.org>. Accessed June 1, 2004.
7. Brignole-Baudouin F, Baudouin C, Aragona P, et al. A multicentre, double-masked, randomized, controlled trial assessing the effect of oral supplementation of omega-3 and omega-6 fatty acids on a conjunctival inflammatory marker in dry eye patients. *Acta Ophthalmol*. 2011;89:e591–e597.
8. Wojtowicz JC, Butovich I, Uchiyama E, et al. Pilot, prospective, randomized, double-masked, placebo-controlled clinical trial of an omega-3 supplement for dry eye. *Cornea*. 2011;30:308–314.
9. Torres LF, Sancho C, Tan B, et al. Early postoperative pain following Epi-LASIK and photorefractive keratectomy: a prospective, comparative, bilateral study. *J Refract Surg*. 2007;23:126–132.
10. Tan BU, Purcell TL, Nalgirkar A, et al. Photorefractive keratectomy for the correction of residual refractive error with Intacs intrastromal corneal ring segments in place. *J Cataract Refract Surg*. 2008;34:909–915.
11. Lichtinger A, Purcell TL, Schanzlin DJ, et al. Gabapentin for postoperative pain after photorefractive keratectomy: a prospective, randomized, double-blind, placebo-controlled trial. *J Refract Surg*. 2011;27:613–617.
12. Saad HA, Terry MA, Shamie N, et al. An easy and inexpensive method for quantitative analysis of endothelial damage by using vital dye staining and Adobe Photoshop software. *Cornea*. 2008;27:818–824.
13. *Statistica for Windows* [computer program]. Version 9.1, Tulsa, OK: Statsoft; 2009.
14. Srinivasan BD. Corneal reepithelialization and anti-inflammatory agents. *Trans Am Ophthalmol Soc*. 1982;80:758–822.
15. Matt C. Fish oil benefits and side effects from answer fitness. Available at: <http://www.answerfitness.com/139/fish-oil-supplements-benefits-side-effects-answer-fitness/>. Accessed September 7, 2012.
16. Macsai MS. The role of omega-3 dietary supplementation in blepharitis and meibomian gland dysfunction (an AOS thesis). *Trans Am Ophthalmol Soc*. 2008;106:336–356.
17. Foster CS. Dry eye syndrome, eMedicine ophthalmology. Available at: <http://emedicine.medscape.com>. Accessed February 15, 2011.