Efficacy of omega-3 in treatment of recurrent aphthous stomatitis and improvement of quality of life: a randomized, double-blind, placebo-controlled study

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Objective. This study assessed the effects of systemic omega-3 on the treatment of recurrent aphthous stomatitis and on the improvement of quality of life.

Study Design. Fifty participants were randomly assigned to receive either omega-3 (1 g, 3 times daily) or placebo for 6 months. Assessment of outcome measures including monthly number of new ulcers, average duration of ulcer episodes, and pain level of ulcers was carried out at baseline and monthly for 6 months. Analysis of potential impact on quality of life using the Oral Health Impact Profile 14 was carried out at baseline and 6 months.

Results. Daily omega-3 treatment achieved a significant reduction in number of ulcers, duration of ulcers, and level of pain by 3 months that persisted for 6 months. Mean score on Oral Health Impact Profile 14 also significantly improved by 6 months.


Recurrent aphthous stomatitis (RAS) is a multifactorial chronic inflammatory disorder that may be classified into 3 clinical variants (minor, major, and herpetiform), of which the most common by far is minor aphthous ulceration.\textsuperscript{1} Several studies have demonstrated the role of immunologic factors, stress, trauma, cessation of smoking, and luteal phase of the menstrual cycle in the etiopathogenesis of RAS.\textsuperscript{2} The goals of current therapeutic approaches include the management of pain and functional impairment, as well as reducing the duration and frequency of recurrences. To achieve these goals, several medicaments for topical use have been used, including chlorhexidine, hyaluronic acid, and amlexanox, with different and not always reproducible results.\textsuperscript{3-5} In RAS patients who do not respond to topical therapy, the use of systemic medications should be considered, including corticosteroids, levamisole, or colchicine.\textsuperscript{6,7} However, the therapeutic value of current systemic therapies with respect to the development of adverse effects remains unproven, and the search for effective and well-tolerated systemic agents to enhance treatment options for clinicians continues.

Recent studies have investigated the beneficial effects of fish oils as rich dietary sources of the omega-3 polyunsaturated fatty acids eicosapentaenoic acid (EPA) (20:5\textsubscript{ω3}) and docosahexaenoic acid (DHA) (22:6\textsubscript{ω3}) on chronic inflammatory diseases including rheumatoid arthritis, systemic lupus erythematosus, inflammatory bowel diseases, and chronic periodontitis.\textsuperscript{8-11} Although several studies have suggested that dietary supplementation with a dose of about 1.5 g/d of EPA/DHA is sufficient to control inflammatory processes, others have recommended higher doses (e.g., 3.5 g/d).\textsuperscript{12}

Recurrent oral mucosal lesions including RAS can cause a wide range of clinical signs and symptoms, some of which can have a considerable effect on quality of life.\textsuperscript{13} However, studies investigating this effect are still lacking. This study was initiated to evaluate the potential of dietary supplementation of omega-3 polyunsaturated fatty acids for providing an inexpensive, safe, and effective therapeutic agent for managing RAS.

MATERIALS AND METHODS

Subjects and study design

This parallel-design, double-blind, placebo-controlled study was conducted on 50 participants divided randomly into a control group (placebo group) that included 25 participants (10 males and 15 females) who received placebo soft gelatin capsules and an

Statement of Clinical Relevance

Findings from this double-blind, randomized, placebo-controlled study of 50 participants supported the potential of omega-3 polyunsaturated fatty acids for providing a safe, inexpensive, and effective therapy for recurrent aphthous stomatitis and improving the quality of life in affected patients.
experimental group (omega-3 group) that included 25 participants (12 males and 13 females) who received omega-3 soft gelatin capsules of 1000 mg each (Super Omega; Technopharma, Cairo, Egypt). The participants were selected from patients of the outpatient clinic of the Oral Medicine and Periodontology Department, Faculty of Dentistry, October 6 University. The research was conducted between April 2012 and May 2013, and participants were recruited from April 2012 to September 2013. The study complied with the Helsinki Declaration of 1964, as revised in 2004, and the protocol was approved by the relevant research ethics committee. Each participant attended clinic visits at the time of randomization (baseline) and at 1-month intervals for 6 months. Eligible participants (both male and female) fulfilled the following criteria: being older than 13 years of age; having recurrent minor aphthous ulcer for at least 1 year with a frequency of at least 1 outbreak per month; presenting with 1 to 3 aphthous ulcers (of less than 48 hours’ duration) with a size no greater than 5 mm in diameter; having normal sense of pain, without anesthesia or paresthesia; and being willing to participate in the study and sign the informed consent form. We excluded individuals who had concurrent clinical conditions that could pose a health risk to the participants, including serious heart, liver, or kidney dysfunctions; pregnancy or lactation; ulcers as a manifestation of systemic disorders such as ulcerative colitis, Crohn disease, Behçet syndrome, or serious anemia; use of medications such as systemic steroids, immunomodulatory agents, antibiotics, or nonsteroidal anti-inflammatory drugs (except occasional use for headaches) within 1 month before study entry; or participation in any other clinical trials within 3 months before study entry. Participants who met the inclusion/exclusion criteria received full written and verbal information about the study and signed the informed consent form. They were assigned numbers in ascending order and were randomly divided by a computer-generated table to receive 1 of the 2 treatments. A randomized block design was used to prepare the randomization table that was sent to the university’s pharmacy, which prepared identical-looking coded dark bottles of medication. Each omega-3 capsule provided 200 mg of DHA prepared identical-looking coded dark bottles of medication. Each omega-3 capsule provided 200 mg of DHA.

An extra number of capsules were put in each bottle. During the 3-month and 6-month follow-ups, the unused medications were collected and counted. At the end of the 3-month appointment, each participant received his or her medication for the remaining 3 months from the study coordinator.

At baseline appointment, each participant was asked to estimate the monthly number of new ulcer outbreaks, the average level of pain using a visual analog scale (VAS), and the average duration of ulcer episodes per month during the past year. To evaluate treatment effectiveness, each participant met the research staff once per month for the duration of his or her enrollment (6 months) to report the monthly average of these parameters. These data were collected by a separate investigator (E.A.G.), who remained masked to treatment allocation. The enrolled subjects were instructed to report the emergence of any adverse events and their relationships to the used study medication. Measurements of oral health—related quality of life were carried out at baseline and at 6 months using the Arabic version of the Oral Health Impact Profile 14 (OHIP-14) questionnaire. For completing the questionnaire, each participant was asked about the frequency with which he or she had experienced an impact on 14 daily activities, and responses were made on a 5-point Likert-type scale (never, hardly ever, occasionally, fairly often, and very often). The additive scores for the OHIP-14 were obtained by summing the response codes to the 14 items constituting the measure. During filling of the questionnaires, each participant was assisted by one of the research team members, who was blinded to the participant’s group assignment. This was done to optimize comprehensibility of the instrument and minimize the probability of having uncompleted questionnaires.

Statistical analysis

Data in the present study were presented as mean and standard deviation (SD), were explored using the Kolmogorov-Smirnov test of normality, and were found to have a normal (parametric) distribution. The comparisons between the 2 study groups were determined by using an independent-samples t test. Moreover, within each group, a paired-sample t test was used to determine significant changes between the baseline and different follow-up points for parametric data. The level of significance was established at a value of \( P < .05 \). We estimated the sample size according to the expected difference in the VAS pain scores between groups. In a previous pilot study (10 cases for each group), we found that the SD for the control group was 2.1, the SD for the test group was 2.27, and the mean difference between the 2 groups was 1.5. Therefore, the calculated minimal sample size was 23 cases in each group, with
RESULTS

Fifty participants (22 males and 28 females) completed the study. 25 in the placebo group (mean age, 32.52 ± 13.84 years) and 25 in the omega-3 group (mean age, 33.68 ± 14.56 years). For age and gender, no significant difference was found between the 2 groups (P > .05; Table I).

The results from the placebo group showed that there was no statistically significant difference in the mean of monthly number of new ulcers, average VAS score, average duration of ulcer episodes, and mean of the total OHIP-14 scores at any of their assessment points as compared with baseline values (Tables II, III, IV, and V). The omega-3 regimen resulted in sustainable beneficial effects on all clinical parameters at 3, 4, 5, and 6 months, as well as OHIP-14 at the 6-month follow-up, as compared with baseline values (see Tables II, III, IV, and V).

Regarding intergroup comparisons, the baseline data of the 2 groups did not show significant differences in the mean of the tested clinical variables or in the mean of the OHIP-14 scores (P > .05; see Tables II, III, IV, and V). Also, intergroup comparisons showed that the differences in the mean number of monthly ulcer outbreaks, average VAS score, and duration of ulcer episodes per month at 1 and 2 months after treatment start were not significantly different between groups (P > .05). However, for the 3-, 4-, 5-, and 6-month follow-up appointments, the results showed significant difference between the 2 groups (see Tables II, III, and IV), which was suggestive of sustainable beneficial effects of omega-3 therapy. Data collected at the 6-month follow-up revealed significant improvement in the mean of the total OHIP-14 scores in the omega-3 treatment group (P < .01; see Table V).

It is important to note that in the present study all participants returned for scheduled follow-up visits. There were neither dropouts nor major deviation in the use of medication. Moreover, no adverse effects of the used medication were reported to the study coordinator.
TABLE V. OHIP-14 scores (mean ± SD) in the 2 study groups at baseline and at 6-month follow-up

<table>
<thead>
<tr>
<th>Function limitation items</th>
<th>Placebo (n = 25)</th>
<th>Omega-3 (n = 25)</th>
<th>Placebo (n = 25)</th>
<th>Omega-3 (n = 25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.16 ± 2.59</td>
<td>3.32 ± 2.44</td>
<td>1.88 ± 1.39</td>
<td>1.40 ± 1.08</td>
<td></td>
</tr>
<tr>
<td>1.64 ± 1.52</td>
<td>1.64 ± 1.49</td>
<td>1.04 ± 1.05</td>
<td>0.68 ± 0.74</td>
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</tr>
<tr>
<td>1.56 ± 1.41</td>
<td>1.68 ± 1.54</td>
<td>0.84 ± 0.89</td>
<td>0.72 ± 0.79</td>
<td></td>
</tr>
<tr>
<td>3.96 ± 2.05</td>
<td>3.80 ± 2.61</td>
<td>3.72 ± 2.27</td>
<td>1.52 ± 1.53</td>
<td></td>
</tr>
<tr>
<td>2.36 ± 1.15</td>
<td>2.28 ± 1.60</td>
<td>2.16 ± 1.37</td>
<td>0.84 ± 0.89</td>
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<tr>
<td>1.60 ± 1.25</td>
<td>1.60 ± 1.52</td>
<td>1.56 ± 1.80</td>
<td>0.72 ± 0.93</td>
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<tr>
<td>2.56 ± 2.59</td>
<td>2.64 ± 2.75</td>
<td>2.56 ± 1.78</td>
<td>1.16 ± 0.85</td>
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<tr>
<td>1.12 ± 1.48</td>
<td>1.28 ± 1.67</td>
<td>1.24 ± 1.45</td>
<td>0.84 ± 0.58</td>
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<tr>
<td>1.44 ± 1.44</td>
<td>1.36 ± 1.55</td>
<td>1.32 ± 1.21</td>
<td>0.68 ± 0.69</td>
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</tr>
<tr>
<td>2.88 ± 2.68</td>
<td>2.40 ± 2.44</td>
<td>2.32 ± 2.60</td>
<td>0.09 ± 0.84</td>
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</tr>
<tr>
<td>1.32 ± 1.34</td>
<td>1.04 ± 1.51</td>
<td>1.04 ± 1.39</td>
<td>0.44 ± 0.50</td>
<td></td>
</tr>
<tr>
<td>1.56 ± 1.52</td>
<td>1.36 ± 1.68</td>
<td>1.28 ± 1.51</td>
<td>0.56 ± 0.65</td>
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</tr>
<tr>
<td>1.92 ± 2.25</td>
<td>2.28 ± 2.62</td>
<td>2.16 ± 2.21</td>
<td>1.36 ± 1.31</td>
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<tr>
<td>1.08 ± 1.18</td>
<td>1.16 ± 1.54</td>
<td>1.08 ± 1.46</td>
<td>0.64 ± 0.81</td>
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<tr>
<td>0.92 ± 1.28</td>
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<td>0.72 ± 0.93</td>
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<tr>
<td>1.76 ± 2.50</td>
<td>2.12 ± 2.63</td>
<td>1.88 ± 2.24</td>
<td>1.20 ± 1.11</td>
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<tr>
<td>1.04 ± 1.39</td>
<td>1.24 ± 1.50</td>
<td>1.12 ± 1.53</td>
<td>0.64 ± 0.75</td>
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<tr>
<td>0.72 ± 1.24</td>
<td>0.88 ± 1.33</td>
<td>0.76 ± 1.33</td>
<td>0.56 ± 0.76</td>
<td></td>
</tr>
<tr>
<td>1.44 ± 2.12</td>
<td>1.52 ± 2.14</td>
<td>1.48 ± 1.75</td>
<td>0.88 ± 1.26</td>
<td></td>
</tr>
<tr>
<td>0.76 ± 1.30</td>
<td>0.56 ± 1.12</td>
<td>0.56 ± 0.96</td>
<td>0.40 ± 0.70</td>
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</tr>
<tr>
<td>0.68 ± 1.14</td>
<td>0.96 ± 1.27</td>
<td>0.92 ± 1.03</td>
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</tr>
<tr>
<td>17.80 ± 13.7</td>
<td>18.16 ± 14.47</td>
<td>16.00 ± 10.07</td>
<td>8.64 ± 5.80</td>
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</tbody>
</table>

DISCUSSION

The worldwide distribution, high frequency, and decreased quality of life of recurrent aphthous stomatitis have resulted in a great deal of research into the etiology and efficient therapy of this condition. Various treatment modalities have been evaluated, of which topical medical products have been the most commonly used to achieve symptomatic relief. However, these agents cannot reduce the frequency of recurrence of the disease. Moreover, some studies have reported that stress management, relaxation, and imagery training may also have additional therapeutic benefits.27 For patients whose symptoms are not alleviated by these primary lines of treatment, systemic medications, including those targeting immune and inflammatory processes involved in the pathogenesis of RAS, have been shown to be effective secondary lines of treatment.18

In this double-blind, placebo-controlled study, the use of 1.5 mg/d of DHA/EPA for 6 months was associated with significant reduction in the number of ulcer outbreaks, the average level of pain, and the duration of ulcer episodes per month starting in the third month of treatment. Moreover, this experimental protocol resulted in improved quality of life in the participants, reflected by the significant reduction in the mean of the total scores of OHIP-14 at the sixth month compared with baseline scores.

Given the inflammatory nature and the involvement of immune mechanisms in the pathogenesis of RAS, our interpretation of these results is that the clinical beneficial effects of the omega-3 regimen could be attributed to the ability of EPA and DHA to alter cellular functions of polymorphonuclear leukocytes (through regulating the trafficking of inflammatory cells to the sites of inflammation and blocking proinflammatory cytokine production), to modulate lymphocyte proliferation, and to significantly increase the activities and mRNA expression of endogenous host antioxidant enzymes including glutathione peroxidase, superoxide dismutase, and catalase, thus enhancing clearance of inflammation within the lesion to promote tissue regeneration.19,22 Furthermore, animal and human studies have demonstrated the ability of omega-3 polyunsaturated fatty acids to competitively inhibit the production of arachidonic acid metabolites via the cyclooxygenase and lipoxygenase pathways. This downregulatory effect may account for the role of EPA and DHA in limiting tissue damage.23,24 In addition, metabolism of omega-3 polyunsaturated fatty acids was found to result in the production of the proresolving lipid mediators, resolvins and protectins, with anti-inflammatory and immunoregulatory actions that can enhance resolution of inflammation and aid in wound healing.25

The results of the present study are in accordance with those reported by Duffy et al.,26 who demonstrated significant beneficial effects of omega-3 fish oil capsules containing 900 mg EPA/DHA administered
daily for 24 weeks on disease activity in patients with systemic lupus erythematosus using the revised Systemic Lupus Activity Measure.\textsuperscript{9} Moreover, our results are in agreement with the results of Preshaw et al.,\textsuperscript{28} who reported a potential therapeutic value of host modulation therapy (subantimicrobial dose of doxycycline, 20 mg twice daily) in the management of patients with recurrent oral aphthous ulceration, including reduction in number of new ulcer outbreaks and alleviation of symptoms.\textsuperscript{20}

Our results are further supported by the demonstrated clinical therapeutic benefits of colchicine and prednisolone as anti-inflammatory and immunomodulatory agents in the treatment of RAS patients. Both agents significantly improved the size and number of lesions, severity of pain, recurrence, and duration of pain-free episodes.\textsuperscript{7} Moreover, our results are in agreement with those reported by Samet et al.,\textsuperscript{23} who demonstrated that daily ingestion of 500 mg of propolis for at least 6 months achieved a significant reduction in ulcer outbreaks and improvements in quality of life in RAS patients. The authors suggested that the targeting of immune and inflammatory pathways by propolis may be one of the suspected mechanisms in the management of RAS patients.\textsuperscript{27}

Studies have provided evidence that the anti-inflammatory and resolving effects of these omega-3 fatty acids are dose- and time-dependent. However, the dose and time required to prevent or treat inflammatory conditions are not clear.\textsuperscript{28} The American Heart Association has suggested that a dose of 0.5 to 1.8 g/d of EPA + DHA is generally regarded as safe in healthy people. In addition, the American Heart Association guidelines recommend monitoring, by a physician, of people consuming high doses of EPA + DHA (>3 g/d) because of the potential complication of excessive bleeding.\textsuperscript{29} Another factor relevant to this discussion is that recent studies have found an increased risk of prostate cancer among men with high blood concentrations of long-chain omega-3 polyunsaturated fatty acids.\textsuperscript{30} Therefore, recommendations to increase intake of these dietary supplements for disease prevention should consider these potential risks.

**CONCLUSIONS**

The results of this study suggest a potential therapeutic role of omega-3 administration in the management of RAS. Moreover, the demonstrated progressive beneficial effects of the omega-3 regimen over the whole observation period suggest that further studies for extended time periods to evaluate its possible effects are required. Further studies involving larger sample size and different supplement dosages are recommended to test their effectiveness.

**REFERENCES**


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