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The effect of omega-3 on recurrent aphthous stomatitis: a systematic review

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ABSTRACT

Introduction: Recurrent aphthous stomatitis is one of the most common chronic inflammatory diseases of the oral cavity affecting approximately 5 to 25% of the general population. Recently, studies on the beneficial effects of omega-3 have arisen, as they have anti-inflammatory and immunomodulatory characteristics. This review´s aim was to answer the clinical question, "Do omega-3 fatty acids improve the signs and symptoms of recurrent aphthous stomatitis?".
Methodology: The review was registered in PROSPERO and was conducted according to the PRISMA guidelines. The literature research was performed in PubMed, Cochrane Library, Livivo, Lilacs, and Google Scholar in March 2022 and the articles considered were published between 2012 and 2022. The risk of bias of the included studies was performed using the Cochrane risk of bias tool 2.
Results: Omega-3 supplementation decreased the average monthly number of ulcers at 6 months of supplementation and from 3 months onwards the ulcers persisted for less time. There was a reduction in ulcer size and ulcer recurrence at 6 months in two of the studies. With regard to pain, it has improved after 6 months of supplementation.
Conclusion: Supplementation with omega-3 appears to have therapeutic potential in the control of recurrent aphthous stomatitis.

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INFORMAÇÃO DO ARTIGO

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RESUMO

Introdução: A estomatite aftosa recorrente é uma das doenças inflamatórias crónicas mais comuns da cavidade oral, afetando aproximadamente 5 a 25% da população geral. Recentemente, têm surgido estudos sobre os efeitos benéficos dos ácidos gordos ômega-3, dado que apresentam características anti-inflamatórias e imunomoduladoras. O objetivo desta revisão foi responder à seguinte questão clínica: "Os ácidos gordos ômega-3 melhoram os sinais e sintomas da estomatite aftosa recorrente?"

Metodologia: A revisão foi registada na base de dados PROSPERO e foi conduzida de acordo com as diretrizes PRISMA. A pesquisa bibliográfica foi realizada nas bases PubMed, Cochrane Library, Livivo, Lilacs e Google Scholar em março de 2022, e os artigos considerados foram publicados entre 2012 e 2022. A avaliação do risco de viés dos estudos incluídos foi realizada utilizando a ferramenta Cochrane Risk of Bias Tool 2.

Resultados: A suplementação com ômega-3 demonstrou diminuir o número médio mensal de úlceras aos 6 meses de suplementação, e a partir dos 3 meses as úlceras passaram a persistir por menos tempo. Verificou-se também uma redução do tamanho das úlceras e da sua recorrência aos 6 meses em dois dos estudos incluídos. Relativamente à dor, observou-se uma melhoria após 6 meses de suplementação com ômega-3.

Conclusão: A suplementação com ômega-3 parece ter potencial terapêutico no controlo da estomatite aftosa recorrente.

Introduction

Recurrent aphthous stomatitis (RAS) is one of the most common chronic inflammatory diseases of the oral cavity affecting approximately 5 to 25% of the general population, characterized by recurrent episodes of painful, single or multiple, rounded or ovoid ulcers well-defined with erythematous borders and a greyish-yellow halo without association with other systemic diseases, which resolve spontaneously and have a typical onset in childhood or adolescence.[1-6]

The exact etiology and pathogenesis of RAS remain unknown, but it is believed that there are several factors involved in its onset. Among the triggers is genetic predisposition, immunological factors, stress and anxiety, local trauma, hematological deficiencies, hormonal changes, nutritional deficits, food hypersensitivity/allergy and oral flora changes.[3,5,7-9]

Given the diversity of precipitating factors of RAS, various therapeutic methods have been discussed, however, to date, there is no established curative treatment. The aim of therapeutic approaches is to control pain, improve functional limitations and reduce the duration and frequency of ulcer recurrence. Topical and/or systemic drugs such as corticosteroids, topical anesthetics, anti-inflammatory drugs, immunomodulatory agents, antiseptic agents, and LASER therapy have been used to achieve these goals.[3-6,10,11]

In recent decades there have been several epidemiological studies on the beneficial effects of omega-3 polyunsaturated fatty acids (ω-3 PUFAs).[12] The main ω-3 PUFAs are eicosatetraenoic acid (EPA (20:5ω3)) and docosahexaenoic acid (DHA (22:6ω3)) and these possess anti-inflammatory and immunomodulatory characteristics.[6,11,13-16] Both are able to competitively inhibit the production of arachidonic acid (AA) metabolites by the cyclooxygenases and lipoxygenase pathways, thereby decreasing pro-inflammatory AA mediators.[11,13,14,16,17] Additionally, mediators with anti-inflammatory and immunoregulatory action result from the metabolism of ω-3 PUFAs that may enhance the resolution of inflammation and aid wound healing.[15,17,18]

A number of clinical trials have also been conducted in recent years to evaluate the effect of ω-3 PUFAs in the control of RAS, thus the aim of this review was to summarize the available evidence regarding the effect of oral omega-3 fatty acid supplementation on RAS. To fulfil this aim the following clinical question was formulated: "Do omega-3 fatty acids improve the signs and symptoms of RAS?".

Methodology

The study used a quantitative, descriptive-exploratory approach with a cross-sectional design. The sample included 35 adult citizens (ages 18-65), using a convenience sample, residing in the municipality of Lamego, who were present at preselected institutions, with the conditions demanded

for the study and accepted to participate. Participants were informed of the study's aims and voluntarily completed the questionnaire. Data were collected using a structured, self-administered questionnaire consisting of 20 questions divided into three sections: 1) sociodemographic information (gender, age, marital status, educational level, number of children, and professional status); 2) knowledge regarding risk behaviours incorporating questions on health recommendations (e.g. ideal sleep duration, effects of physical inactivity, healthy eating, and risks associated with tobacco and alcohol); and 3) actual behaviours (e.g. food consumption, alcohol, tobacco), evaluated using a Likert scale, comprised of five levels (very poor to excellent).

Results

Search strategy

The PRISMA flow diagram for selecting articles to include in the systematic review is shown in figure 1.[19]

From the databases, 213 potentially eligible articles were found, of which 24 were duplicates, and 7 were not English or Portuguese language and were therefore excluded. After applying the defined inclusion and exclusion criteria to the remaining 182 articles, 4 articles were included in this systematic review. Of these, 3 were placebo-controlled, randomized, double-blind clinical trials,[4,6,10] and 1 was a randomized, unblinded clinical trial.[11] Regarding comparison groups, 3 studies[4,6,10] compared systemic ω-3 PUFAs supplementation with placebo, and the 2018 study by Moawad and colleagues[11] compared systemic ω-3 PUFAs supplementation with low-intensity laser therapy and ω-3 PUFAs supplementation simultaneously.

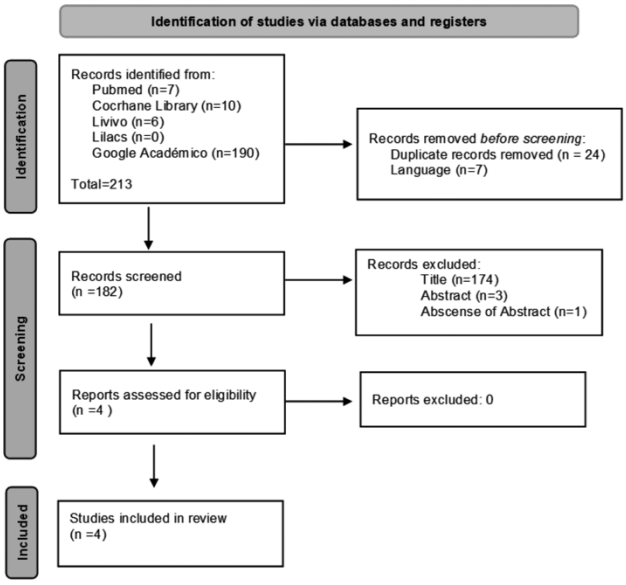

Figure 1. PRISMA flow chart (Research Strategy and Selection of Articles).

Assessment of the risk of bias

The clinical trials included in this systematic review generally present high methodological quality, i.e., low risk of bias. A detailed assessment of the methodological quality of clinical trials is shown in figure 2.

Assessment of the Risk of Bias in Included Clinical Trials

Study ID	Experimental	Comparator	D1	D2	D3	D4	D5	Overall
El-Khouli and El-Gendy., 2014	ômega-3	placebo	+	+	+	+	+	+
Nosratzehi and Akar., 2016	ômega-3	Placebo	+	+	+	+	+	+
Hadian etall., 2021	ômega-3	Placebo	+	+	+	+	+	+
Moawad et all., 2018	ômega-3	Low level LASER Therapy	+	+	+	+	!	!

Key:		D1	Randomisation process
		D2	Deviations from the intended interventions
+	Low risk	D3	Missing outcome data
!	Some concerns	D4	Measurement of the outcome
-	High risk	D5	Selection of the reported result

Figure 2. Cochrane risk of bias tool 2.

Polinsaturated omega-3 fatty acids (PUFAs ω3) and ear

In El Khouli and El-Gendy's 2014 study,[10] results showed that the group receiving omega-3 supplementation showed improvements in the average number of ulcers per month, a decrease in pain, and a reduction in ulcer healing time at 3, 4, 5, and 6 months when compared to baseline and the group receiving placebo.

In 2016, in Nosratzehi and Akar's clinical trial,[4] the group receiving ω-3 PUFAs at six months showed significantly smaller ulcer size than at the start of treatment and, when

compared to the group receiving a placebo. The two groups showed no difference in ulcer size at the start of treatment. The omega-3 group also showed a significant reduction in the number of ulcers at the 4th, fifth, and sixth months of follow-up and a significant decrease in ulcer recurrence, but only at the fifth and sixth months of supplementation compared to the placebo group. The intensity/sensation of pain in the group with omega-3 supplementation at six months was significantly lower than in the group receiving placebo, with no differences between the two groups at the initial assessment.

In the 2021 clinical trial in Iran by Hadian and colleagues,[6] at the first assessment at three months, the group receiving omega-3 showed a decrease in the mean number of ulcers, a decrease in the duration of ulcers, and a reduction in ulcer severity relative to the group receiving the placebo. However, there were no differences between the groups in pain intensity, ulcer size, and ulcer-free time. In the evaluation at six months, there were statistically significant differences between the two groups in all characteristics: decrease in mean number of ulcers, decrease in ulcer duration time, decrease in ulcer severity, decrease in pain intensity, decrease in ulcer size and longer ulcer-free time in the group receiving omega-3.[6]

In the 2018 study by Moawad and colleagues, the group that received LASER therapy alone showed statistically significant differences in reduced ulcer size and decreased pain sensation when compared to the group that received omega-3 alone but did not show statistically significant differences relative to the group that received LASER therapy and omega-3 supplementation. In turn, the group that received LASER therapy and omega-3 supplementation showed statistically significant differences in reducing ulcer size and decreasing pain intensity compared to the group that received only ω-3 PUFAs supplementation.[11]

The group that received only ω-3 PUFAs supplementation, as well as the group that was exposed to LASER therapy and ω-3 PUFAs supplementation, showed at 3, 4, 5, and 6 months follow-up a statistically significant difference in reducing the duration of ulcers and decreasing the number of new outbreaks compared to the group that only received LASER therapy. However, they did not show significant differences between them.[11]

The group that received only LASER therapy showed no statistically significant differences at any assessment points relative to the initial assessment regarding ulcer healing time and number of new outbreaks. On the other hand, the other two groups showed a continuous and progressive reduction in the duration of ulcers and the number of new outbreaks from the third month onwards until the sixth month compared to the initial values.[11]

Table 1. Summarizing the effects of systemic omega-3 supplementation.

EFFECT OF OMEGA-3 SUPPLEMENTATION ON EAR				
	El Khouli and El-Gendy[10] 2014	**Nosratzehi and Akar[4] 2016**	**Moawad *et al.*[11] 2018**	**Hadian *et al.*[6] 2021**
Average number of ulcers per month	Decrease in the average number of ulcers per month at the 3rd, 4th, 5th and 6th month of supplementation	Significant decrease in the number of ulcers at the 4th, 5th and 6th month of supplementation	NA	Decrease in the average number of ulcers at 3 and 6 months of supplementation
Average duration of ulcer episodes	Decrease in the average duration of ulcer episodes at the 3rd, 4th, 5th and 6th month of supplementation	NA	Reduction in the duration of ulcer episodes at 3, 4, 5 and 6 months of supplementation	Reduction in the duration of ulcer episodes at 3 and 6 months of supplementation
Ulcer size	NA	Reduction in ulcer size at 6 months of supplementation	No change at 5 days of supplementation	No change at 3 months, but decreasing in size at 6 months of supplementation
Recurrence of ulcers	NA	Significant reduction in ulcer recurrence at the 5th and 6th month of supplementation	Decrease in the number of new ulcer outbreaks at 3, 4, 5 and 6 months of supplementation	NA
Ulcer free period	NA	NA	NA	No change at 3 months, but increased period without ulcers at 6 months of supplementation
Ulcer Severity	NA	NA	NA	Reduction of ulcer severity at 3 months and 6 months
Pain	Reduction of pain on the 3rd, 4th, 5th and 6th month of supplementation	Significant reduction in pain intensity at 6 months of supplementation	No change at 5 days of supplementation	No change at 3 months, but showed a reduction in pain at 6 months of supplementation

Key: NA: not assessed

Discussion

Despite extensive research on the treatment of RAS, its control remains a challenge, with no curative treatment yet available.[5,21] To date, only a few studies have been conducted to evaluate the effect of systemic omega-3 supplementation on RAS. Based on the formulated clinical question, "Do omega-3 fatty acids improve the signs and symptoms of RAS?" the results of this review show a likely positive effect of omega-3 supplementation in patients with RAS, improving their signs and symptoms at six months of supplementation and decreasing their recurrence.

The studies that evaluated the mean monthly number of ulcers all showed that omega-3 supplementation decreases the mean monthly number of ulcers at six months of supplementation.[4,6,10] Additionally, the studies by El Khouli and El-Gendy, Hadian et al., and Moawad et al.[6,10,11] showed concordant results regarding the reduction of the duration of ulcer episodes from 3 months of supplementation onwards.[6,10,11] The study by Hadian et al. showed a

decrease in ulcer size at six months of supplementation like that seen in the study by Nosratzehi and Akar.[4,6]

Taking into consideration ulcer recurrence, the study by Nostratzehi and Akar, found a decrease in ulcer recurrence from the fifth month of supplementation, while in the study by Moawad et al. it was from the third month.[4,11] Additionally, in the study by Hadian et al. they found an increase in ulcer-free time from 3 months of supplementation.[6] Thus, omega-3 supplementation seems to reduce ulcer recurrence, although there is no agreement on when this improvement begins. In the study by El Khouli and El-Gendy, pain sensation was improved after three months of supplementation.[10] However, in the study by Nosratzehi and Akar, and in that of Hadian et al. the improvement in pain only occurred after six months of supplementation.[4,6]

Given the inflammatory nature and the involvement of immune mechanisms in the pathogenesis of RAS, the beneficial effect of omega-3 supplementation on RAS can be attributed to its anti-inflammatory and immunomodulatory properties.[4,10,13]

In response to tissue injury, polymorphonuclear leukocytes (PMNs) are recruited to the injury site. In turn, they perform phagocytosis of bacteria and/or cellular debris to remove them from the injury site. Consequently, monocyte-derived macrophages are called to the site to phagocytose the apoptotic PMNs and cellular debris, promoting the resolution of acute inflammation.[22]

The ω-3 PUFAs, EPA and DHA, can alter the cellular functions of PMNs by regulating inflammatory cells and blocking the production of pro-inflammatory cytokines to modulate lymphocyte proliferation and significantly increase the activity and mRNA expression of endogenous host antioxidant enzymes, including glutathione peroxidase and superoxide dismutase, thereby contributing to the elimination of inflammation within the lesion and promoting tissue regeneration.[4,6,10,13] In turn, EPA and DHA can competitively inhibit the production of AA metabolites by the cyclooxygenases and lipoxygenases pathway, reducing pro-inflammatory arachidonic mediators and increasing pro-resolutive lipid mediators[6,13,16] which decrease the inflammatory process and aid tissue healing, contributing to the resolution of acute and chronic inflammation.[10,16]

As a result of their various anti-inflammatory and inflammation-resolving actions, increasing the intake of EPA and DHA may have therapeutic potential in diseases involving inflammatory processes.[23-25]

One of the possible explanations for some of the divergences found could be that the studies used different omega-3 supplements because, although they were all 1000mg, in at least two studies, the concentrations of EPA and DHA were different. In the other two studies, this information was not available.

The limitations of this study are related to relatively small samples, non-uniform inclusion criteria in the different studies, and differences in the methodology used to measure some of the outcomes; therefore, this heterogeneity only allows us to make qualitative comparisons of the results. Therefore, further studies must be carried out to evaluate the efficacy of omega-3 in treating RAS with greater accuracy. Although the search strategy was defined a priori and limited to articles published between 2012 and March 2022, we acknowledge that the topic is evolving rapidly. Therefore, more recent studies (from 2022 to 2024) may provide additional insights. We suggest future systematic reviews consider these recent developments, and we recognize this as a limitation of the present study.

Conclusion

According to the reviewed studies, systemic supplementation with omega-3 fatty acids improves the signs and symptoms of RAS. Thus, the available evidence suggests that systemic supplementation with ω-3 PUFAs has therapeutic potential in controlling RAS as a sole therapy or adjunctive therapy to other treatments.

However, the available data are still very scarce; therefore, further studies are needed to more accurately assess the efficacy of its use in the treatment of RAS.

References

1. Belenguer-Guallar I, Jiménez-Soriano Y, Claramunt-Lozano A. Treatment of recurrent aphthous stomatitis: a literature review. *J Clin Exp Dent*. 2014;6(2):e168-e174. https://doi.org/10.4317/jced.51401
2. Ślebioda Z, Szponar E, Kowalska A. Etiopathogenesis of recurrent aphthous stomatitis and the role of immunologic aspects: literature review. *Arch Immunol Ther Exp* (Warsz). 2014;62(3):205-215. https://doi.org/10.1007/s00005-013-0261-y
3. Fontes Vieira, AC, Carmo, CDS, Vieira, GMB, Lima, LA, Cruz, MCFN, Lopes, FF. Tratamento da estomatite aftosa recorrente: uma revisão integrativa da literatura. *Revista da Faculdade de Odontologia – UPF*. 2016;20(3):384-92. https://doi.org/10.5335/rfo.v20i3.4584
4. Nosratzehi T, Akar A. Efficacy of omega-3 in treatment of recurrent aphthous stomatitis: a randomized, double-blind, placebo-controlled study. *Chin J Dent Res*. 2016;19(3):159-164. doi: 10.3290/j.cjdr.a36681. PMID: 27622219.
5. Sánchez J, Conejero C, Conejero R. Recurrent aphthous stomatitis. *Actas Dermosifiliogr (Engl Ed)*. 2020;111(6):471-480. https://doi.org/10.1016/j.adengl.2019.09.006
6. Hadian Z, Karandish M, Abbaszadeh M, et al. Effect of omega-3 on recurrent aphthous stomatitis and improvement of quality of life. *Int J Dent*. 2021;2021:6617575. https://doi.org/10.1155/2021/6617575
7. Hudson J. Recurrent aphthous stomatitis: diagnosis and management in primary care. *J Patient Cent Res Rev*. 2014;1(4):197-200. https://doi.org/10.17294/2330-0698.1040
8. Queiroz SIML, Silva MJ, de Medeiros AMC, et al. Recurrent aphthous ulceration: an epidemiological study of etiological factors,

treatment and differential diagnosis. *An Bras Dermatol*. 2018;93(3):341-346. https://doi.org/10.1590/abd1806-4841.20186228
9. Rivera C, Muñoz-Pastén J, Núñez C, et al. Risk factors for recurrent aphthous stomatitis: a systematic review. *Int J Morphol*. 2021;39(4):1102-1108. https://doi.org/10.4067/s0717-95022021000401102
10. El Khouli AM, El-Gendy EA. Efficacy of omega-3 in treatment of recurrent aphthous stomatitis and improvement of quality of life: a randomized, double-blind, placebo-controlled study. *Oral Surg Oral Med Oral Pathol Oral Radiol*. 2014;117(2):191-196. https://doi.org/10.1016/j.oooo.2013.09.003
11. Moawad RS, Ghalwash DM, Hammad SM, et al. Low level LASER therapy and omega-3 in the management of recurrent aphthous stomatitis. *Egypt Dent J*. 2018;64(4):3391-3405. https://doi.org/10.21608/edj.2018.79056
12. Shahidi F, Ambigaipalan P. Omega-3 polyunsaturated fatty acids and their health benefits. *Annu Rev Food Sci Technol*. 2018;9:345-381. https://doi.org/10.1146/annurev-food-111317-095850
13. Azuma MM, Gomes-Filho JE, Ervolino E, et al. The use of omega-3 fatty acids in the treatment of oral diseases. *Oral Dis*. 2020;28(2):264-274. https://doi.org/10.1111/odi.13667
14. Kruse AB, Khouly I, Lang NP, et al. What is the impact of the adjunctive use of omega-3 fatty acids in the treatment of periodontitis? A systematic review and meta-analysis. *Lipids Health Dis*. 2020;19(1):100. https://doi.org/10.1186/s12944-020-01267-x
15. Watanabe Y, Tatsuno I. Prevention of cardiovascular events with omega-3 polyunsaturated fatty acids and the mechanism involved. *J Atheroscler Thromb*. 2020;27(3):183-198. https://doi.org/10.5551/jat.50658
16. Chatterjee D, Agrawal A, Chatterjee A, et al. Role of adjunct use of omega-3 fatty acids in periodontal therapy of periodontitis: a systematic review and meta-analysis. *J Oral Biol Craniofac Res*. 2022;12(1):55-62. https://doi.org/10.1016/j.jobcr.2021.10.005
17. Kaur M, Kaur R, Arora R. A review of omega-3 and its role in oral diseases. *Int J Adv Res*. 2016;4(9):921-925. https://doi.org/10.21474/ijar01/1562
18. Elagizi A, Lavie CJ, Carbone S, et al. An update on omega-3 polyunsaturated fatty acids and cardiovascular health. *Nutrients*. 2021;13(1):204. https://doi.org/10.3390/nu13010204
19. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021;372:n71. https://doi.org/10.1136/bmj.n71
20. University of York. Centre for Reviews and Dissemination. PROSPERO: International Prospective Register of Systematic Reviews. How to register a systematic review in PROSPERO "Integrity of Data and Prospective Registration." Accessed 2 July 2025 at https://www.crd.york.ac.uk/PROSPERO/help/register
21. Sterne JAC, Savović J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ*. 2019;366:l4898. https://doi.org/10.1136/bmj.l4898
22. Halboub E, Al-Mudaffer M, Al-Zubairi L, et al. Zinc supplementation for prevention and management of recurrent aphthous stomatitis: a systematic review. *J Trace Elem Med Biol*. 2021;68:126811. https://doi.org/10.1016/j.jtemb.2021.126811
23. Ishihara T, Yoshida M, Arita M. Omega-3 fatty acid-derived mediators that control inflammation and tissue homeostasis. *Int Immunol*. 2019;31(9):559-567. https://doi.org/10.1093/intimm/dxz001
24. Djuricic I, Calder PC. Beneficial outcomes of omega-6 and omega-3 polyunsaturated fatty acids on human health: an update for 2021. *Nutrients*. 2021;13(7):2421. https://doi.org/10.3390/nu13072421
25. Rivera C. Essentials of recurrent aphthous stomatitis. *Biomed Rep*. 2019;11(2):47-50. https://doi.org/10.3892/br.2019.1221