SYSTEMATIC REVIEW

The Role of Omega 3 as a Host Modulation Therapy (HMT) in Periodontal Tissue Regeneration: A Systematic Review

Hasanuddin Thahir[1], Arni Irawaty Djais[1], Febrianty Syukur[2]

[1] Department of Periodontology, Faculty of Dentistry, Hasanuddin University, Makassar, Indonesia
[2] Program of Educational Specialist Periodontology, Faculty of Dentistry, Hasanuddin University, Makassar, Indonesia

ABSTRACT

Introduction: Host Modulation Therapy is a treatment that promotes tissue repair by suppressing the host's inflammatory response and increasing tissue repair. The purpose of this research is to provide a focused study of periodontal regeneration using Omega-3 as an HMT. **Methods:** The Pubmed and Cochrane databases were searched for randomized control clinical trials published within the last ten years using the following criteria: [(Periodontitis OR Periodontal Disease) AND (Omega-3) AND (Bleeding on Probing OR Pocket Depth)]. The values of Bleeding on Probing and Pocket Depth are used to assess the outcome. Only five studies out of 34 were found to meet the criteria. In four of the five studies involved, the results showed a significant reduction in Bleeding on Probing and Pocket Depth. **Conclusion:** Omega-3 fatty acids have a positive effect on periodontal wound healing by reducing Bleeding on Probing and Pocket Depth.

Keywords: Host Modulation Therapy, Omega-3, Periodontitis, Regeneration Periodontal

Corresponding Author:
Hasanuddin Thahir, Sp. Perio (K)
Email: hasanuddin.thahir@gmail.com
Tel: +62 82344663131

INTRODUCTION

In today's culture, periodontal disease is a common concern in the field of dentistry and oral health. The national prevalence of dental and oral health disorders was 57.4% in 2018, according to the Indonesian Nationwide Basic Health Research Agency (Riskesdas). According to a 2019 report by Gautam, periodontal disease is the world's 11th most common ailment. Periodontal disease is caused by a bacterial infection of periodontal tissue. Periodontitis is the medical term for this type of condition (1,2).

Periodontitis is a public dental health concern that affects approximately 10-15% of the adult population, with 25% of them experiencing mild to severe symptoms, making it a chronic condition. The metabolism of a large amount of bacteria that has accumulated on the tooth surface and supporting tissue is thought to be the cause of periodontitis. In the early stages of periodontitis, the gingiva exhibits localized inflammation. When the gums swell and bleed, there is no loss of connection to the bone-supporting tissue. Inflammation activates inflammatory mediators, as well as cells that play a role in the inflammatory process. (1,3).

The tissue regeneration process begins once the inflammatory process is complete. The regeneration process includes the creation of new cells and intercellular substances, as well as the differentiation of existing tissue components. The type of tissue produced by regeneration will be the same as the type of tissue produced by the injury. Periodontal tissue regeneration in the periodontal field is a condition in which epithelial damage to the gingiva regenerates into new epithelium, while connective tissue and the periodontal ligament regenerate into connective tissue, which is the precursor tissue for both. The creation of new connective tissue is indicated by an increase in the number of fibroblasts in the cell (4).

Although the role of dental plaque in the development of periodontitis is widely acknowledged, the host immune system has recently been identified as one of the etiologies of the inflammatory process and its subsequent damage. As a result, host modification therapy in periodontal care has shifted to an anti-infective approach. In addition to bacteria, other studies suggest that uncontrolled excessive

production of pro-inflammatory cytokines is the main pathophysiology of tissue injury. The amount of bacteria present in clinical trials does not correlate with the degree of damage; however, it cannot be denied that the presence of bacteria is the first etiology of the periodontitis process, followed by its hypothesized variables that trigger the host immune response. Changes in the number of microorganisms, an insufficient host defense milieu, and oxidative stress can all contribute to inflammation. During the pathogenesis process, pro-inflammatory cytokine agents and reactive oxygen species (ROS) can do two things at the same time: they can block bacterial invasion from outside the tissue while also causing additional harm due to over-response of these molecules (5).

Excessive injury to normal tissue may result in a long-term inflammatory response with systemic consequences. Furthermore, if the inflammatory response persists, wound healing will be hampered, necessitating effective prophylaxis to avoid further injury. One type of preventive measure is to use Host Modulation Therapy (5–7).

HMT is a type of therapy that aids in the reduction of tissue damage while also stabilizing or regenerating tissue without interfering with normal or inflammatory defense processes. In cases of periodontitis, the goal of therapy is to inhibit the stimulation of the inflammatory process by using specific pro-resolution mediators such as Omega-3 (5–7).

Omega-3 is an essential fatty acid found in fish oil. Omega-3 fatty acids such as eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), and arachidonic acid (AA) help to prevent pro-inflammatory agents from becoming activated (6–8).

This literature aims to filters targeted study of regeneration periodontal that uses Omega-3 as a Host Modulaion Therapy.

MATERIALS AND METHODS

In this study, the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) guidelines for systematic reviews were followed. With the provided search keyword, a total of 34 papers were discovered in the database search, nine from PubMed and 25 from Cochrane. Following a review of the titles and abstracts, 26 papers were eliminated based on the following criteria: eight duplicates, four irrelevant articles, and 14 full-text articles that were not accessible. The analysis of the abstracts yielded eight potential articles. Among the possible articles, three did not meet the inclusion criteria. As a result, five studies are included in this systematic review (Fig. 1)

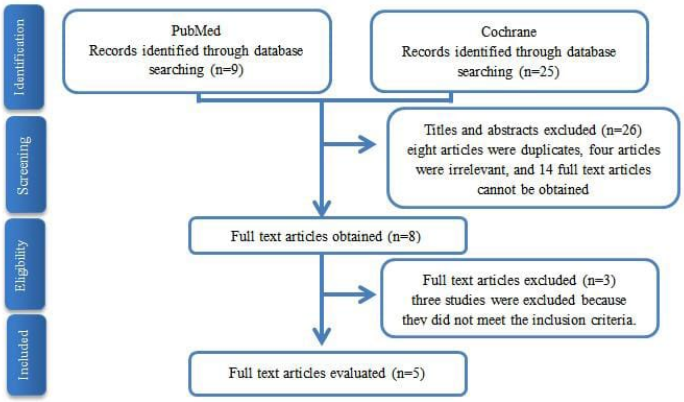

Fig. 1 : PRISMA flowchart.

Focused Question (PICO)

The PICO approach was used to find data articles, and the following criteria were used:

Problem : Patient with periodontitis or periodontal disease
Intervention : Omega-3
Comparison : Scalling Root Planning group with dietary Omega-3 intake and group of Scalling Root Planning with placebo
Outcomes : Bleeding on Probing; Pocket Depth.

The main question of the study was whether using Omega-3 as a Host Modulation Therapy (HMT) has any effect on periodontal tissue regeneration when compared to a placebo group.

Search Strategy

All identified references were culled from two databases: PubMed (www.pubmed.gov) and the Cochrane Library (www.thecochranelibrary.com), and were screened to include only full-text randomized control trial and clinical trial human studies published in English between January 2011 and April 2021. Some search terms are [(periodontitis OR periodontal disease) AND (Omega-3) AND (Bleeding on Probing OR Pocket Depth)]. The title, abstract, and full-text were examined to identify the relevant studies.

Criteria for Study Inclusion and Exclusion

This review focuses on articles containing randomized controlled trials (RCTs) that meet the following criteria: English-language articles, human clinical research, Omega-3 fatty acids in nonsurgical and surgical periodontal therapy, and periodontal diseases such as probing depth (PD) and Bleeding on Probing (BOP). Periodontitis or gingivitis studies, case reports, book articles, article reviews, duplicate

publications, and original articles with only abstracts and no full papers were all removed.

Risk of Bias

The risk of bias is determined by examining the validity, credibility, and quality of each study provided, which are rated as high, medium, or low (Cochrane Handbook for Systematic Review of Intervention). If all of the criteria for the studies are met, they are labeled as having a low risk of bias. The risk of bias is moderate when one of these criteria is missing; when two or more are missing, the risk of bias is high.

Data Extraction

The authors independently reviewed and chose the publications by screening the title and abstract for specific keywords. The full text of each publication relevant to the topic of this systematic review was retrieved and assessed using the inclusion criteria that were developed to produce the final list of articles. The reviewers independently extracted the year of publication, study design, sample size, intervention group and placebo, and early healing index values at baseline and three months after Omega-3 food intake.

RESULTS

Included Study

Following a review of the literature, six studies that discussed Omega-3 as an adjunct therapy in periodontitis patients with Bleeding on Probing (BOP) and Pocket Depth (PD) were identified, as shown in Table I.

Comparison of the Result

Five trials were reviewed in this article, and the findings indicated that Omega-3 could significantly reduce periodontal disease in experimental groups when compared to placebo groups (Table. II)

DISCUSSION

Several studies on current principles in periodontitis pathophysiology and therapy have been conducted. According to Sulijaya et al., gingivitis is the first stage of periodontitis (5). Gingivitis is caused by the accumulation of supragingival plaque, which causes nonspecific inflammatory reactions in the tissues. The presence of an inflammatory process in gingival crevicular fluid has changed the subgingival environment, increasing the concentration of inflammatory mediators and tissue damage products. As a result of this scenario, more dangerous bacteria thrive in the subgingival biofilm. Gingivitis can develop only if the host's inflammatory response, environmental conditions, and hereditary factors all work together. If the host immunological and inflammatory responses are not in good shape, as well as the presence of host genetic variables that aggravate the inflammatory process, gingivitis will progress to periodontitis (5).

Based on this approach, several studies on novel periodontitis treatment options have been conducted. The researchers discovered that by limiting the supply of microbial nutrients and modulating the host's inflammatory response to gingivitis, the subgingival environment can be altered (especially

Table I : Comparison of Study Design

List of Studies	Parameters of studies					
	Type of Study	Number of partici-pants/age	Study period	Dosage of Omega 3	Clinical Periodontal Parameter	
					BOP	PD
Elkhouli AM (2011)[13]	RCT	40 Patients /35-60 years	Baseline, 3 months, and 6 months	1000 mg (300 mg DHA, 150 mg EPA)	Yes	Yes
Martinez GL et. al (2014)[16]	RCT	21 patiens /38-59 years	Baseline, and 4 months	1000 mg (180 mg EPA, 120 mg DHA)	Yes	Yes
Girish D. Deore et. al (2014)[17]	RCT	30 patients /30-60 years	Baseline, 6 weeks, and 12 weeks	300 mg (120 mg DHA, 180 mg EPA)	Yes	Yes
J.P. Woelber et. al (2017)[18]	RCT	15 patients /23-70 years	2 Weeks, 8 Weeks	1000 mg	Yes	Yes
Mirella Stando et. al (2020)[10]	RCT	40 patients /22-70 years	Baseline and 3 months	300 mg	Yes	Yes

*BOP : Bleeding on probing PD : Pocket depth RCT : Root Canal Treatment
DHA : Docosahexaenoic acid EPA : Eicosapentaenoic acid

acakaralotic pathogenic microbiota which can reduce bacterial collagen peptides, where the energy source comes from amino acids). As a result of managing the inflammatory response, the infection process can be suppressed, and an environment conducive to bacterial dysbiosis can be created, allowing commensal bacteria to thrive in the oral cavity's periodontal environment (5).

This study looks at the effect of Omega-3 fatty acids as a dietary source that can be used as part of a Host Modulation Therapy (HMT) to aid periodontal tissue regeneration. A randomized clinical trial study was used to describe the use of Omega-3 as a therapeutic agent in the regeneration process in Table I. The five articles compare the effects of changes in BOP and PD values on the efficacy of Omega-3 fatty acids.

Table II summarizes the use of Omega-3 fatty acids in five different articles by examining their effectiveness on changes in BOP and PD values. When periodontal therapy with Omega-3 fatty acids was compared to placebo, two of the five studies included in the literature showed a significant increase in the computation of Bleeding on Probing and Pocket Depth values. The other two studies only found a reduction in Pocket Depth but no reduction in Bleeding on Probing, and one study found no difference in BOP or PD between the test and placebo groups.

Woelber et al and Stando et al discovered in their study that using Omega-3 can aid in the process of periodontal tissue regeneration, with a statistically significant decrease in BOP and PD values in the test group when compared to the placebo group. This is also consistent with the findings of Eleonora et al., who discovered that Omega-3 and Omega 6 had an anti-inflammatory effect on periodontal disease by directly inhibiting MMP activity. Marie-Odile Huson et al. discovered that Omega-3 fatty acids are effective against extracellular pathogens such as Streptococcus Pneumoniae, Pseudomonas Aeruginosa, Escherichia Coli, and Staphylococcus Aureus in reducing inflammation and lowering the incidence of pneumococcal infection in the elderly (7,9–11).

Omega-3 fatty acids can be used as part of a Host Modulation Therapy that aims to prevent future inflammatory processes and accelerate tissue regeneration (Fig. 2). Omega-3 contains a variety of fatty acids, including AA, EPA, and DHA. Although arachidonic acid is pro-inflammatory, EPA and DHA have anti-inflammatory and immunomodulatory properties that aid in inflammation reduction. The EPA and DHA content of enteral and parenteral products is affected by the amount of Omega-3 fatty acids in various types of Omega-3 dietary intake. Inflammation and improper immunosuppression are caused by surgery, trauma, and infection, and can progress to sepsis and septic shock.

Table II : Comparison of the result of studies

List of Studies	Period of Studies	Clinical Periodontal Parameter		Result
		Bleeding on Probe	Pocket Depth	
Elkhouli AM (2011) [13]	Baseline	1.61±0.48	5.6±0.8	Values were not determined in BOP and statistically significant reduction of PD in the test group
	3 Months	0.59±0.22	3.7±0.8	
	6 Months	0.48±0.24	3.4±0.6	
Martinez GL et. al (2014) [16]	Baseline	20.06(58.3)	69.5(46.0)	No change in BOP and PD compared test group and placebo group
	4 Months	5.5(23.0)	92.0(35.0)	
Girish D. Deore et. al (2014) [17]	Baseline	2.52±0.38	4.26±1.10	Values were not determined in BOP and statistically significant reduction of PD in the test group
	6 Weeks	1.65±0.28	2.61±0.53	
	12 Weeks	1.41±0.30	2.15±0.53	
J.P. Woelber et. al (2017) [18]	2 Weeks	53.57(18.65)	2.19(0.34)	Statistically significant reduction of BOP and PD in the test group
	8 Weeks	24.17(11.57)	2.11(0.35)	
Mirella Stando et. al (2020) [10]	Baseline	28±16	55±29	Statistically significant reduction of BOP and PD in the test group
	3 Months	14±6	32±21	

*BOP : Bleeding on probing PD : Pocket depth

Hyperinflammation is distinguished by the production of inflammatory cytokines such as eicosanoid from arachidonic acid and other inflammatory mediators, whereas immunosuppression is distinguished by decreased antigen release and lymphocyte response T-helper type 1 (12-15).

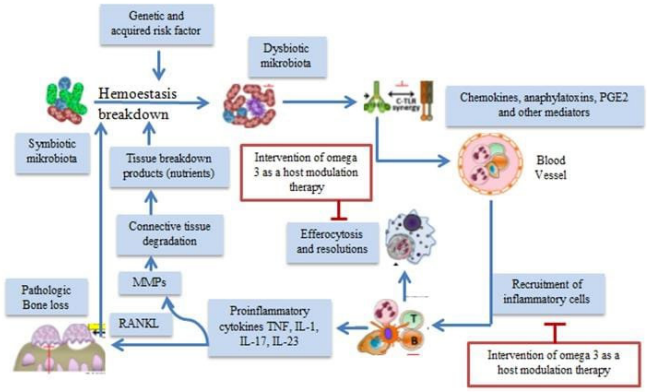

Fig. 2 : Omega-3 as a periodontitis Host Modulation Therapy. Periodontitis is caused by a disruption in the balance between the number of symbiotic in the oral cavity and the host's immune system's inability to fight infections in the body. Dysbiosis and inflammation not only activate osteoclastogenesis and bone loss, but also increase the production of nutrients in the blood, allowing microbial disbiotics to become more developed and penetrating. Omega-3 is depicted as a potential intervention and therapeutic target, the majority of which are still in the experimental stage. Omega-3 as a pro-resolution mediator agent, specifically in Host Modulation Therapy against periodontitis; Omega-3 as a therapeutic modulation host during the periodontitis process occurs, in this case Omega-3 which is contained on EPA and DHA functions to reduce inflammation, which can terminate further neutrophil recruitment involves their ability to upregulate endogenous inhibitors of neutrophil recruitment. TNF, tumor necrosis factor; C, complement; IL, interleukin; MMPs, matrix metalloproteinases; PGE2, prostaglandin E2; RANKL, receptor activator of nuclear factor-kappaB ligand (tumor necrosis factor ligand superfamily member 11); TLR, toll-like receptor.

Omega-3 supplementation is a simple strategy for improving periodontitis treatment in both the short and long term. Given the growing problem of antibiotic resistance, alternative antibiotic treatment during periodontal therapy is also required. Taking Omega-3 in the form of fish oil capsules is considered simple in periodontal therapy, and the treatment is not prohibitively expensive. According to various studies, the daily intake of EPA and DHA for healthy people who do not have cardiovascular disease is 500 mg, and for patients who do have cardiovascular disease is 1000 mg. In the study discussed in this article, the daily dose ranged between 300 mg and 1000 mg. A review of available studies found that when the dose of Omega-3 used was less than 300 mg, the results showed a significant increase in BOP and PD values when compared to trials using the highest dose of 3000 mg. The use of high doses of Omega-3 in Martinez et al study .'s with a dose of Omega-3 twice a day did not show a significant influence on changes in BOP and PD values. The amount of time spent using Omega-3, in addition to the dose, can have an effect on the therapy's outcomes. Eating two servings of fatty marine fish per week is enough to meet the daily requirement of 300 mg of EPA/DHA, according to nutritional health data. Higher levels can be gained by eating a balanced and rich fish diet, as well as eating Omega-3 fortified foods like yogurt, margarine, and eggs, as well as taking dietary supplements (10,16).

According to Chee et al., many recent studies have been conducted to learn more about various host modulating agents, such as selective COX-2 inhibitors, bisphosphonates and statins, as well as tetracyclines and macrolide antibiotics, that can be used as single therapy or adjunct treatment for periodontitis. New therapeutics are also being developed for the RANKL-OPG system, pro-inflammatory cytokines, and cell signaling pathways such as NF-B, Mitogen-Activated Protein Kinase (MAPK), and Tyrosine Kinase-signal Transducer and Transcription Activator (JAK-STAT). However, several of these medications have been shown to have side effects that significantly impair periodontal treatment healing function, such as immunosuppression, gastrointestinal bleeding difficulties, and kidney and liver abnormalities (18).

CONCLUSION

According to the findings of the literature review, using Omega-3 as a Host Modulation Therapy (HMT) can significantly increase periodontal tissue regeneration while decreasing Bleeding on Probing and Pocket Depth. More research is needed into the relationship of Omega-3, particularly Omega-3 derived directly from fish oil, as a natural food additive that can aid in the repair of inflammatory tissue, so that this food source can be used as an alternative treatment, specifically as a host modulation theraphy, based on the discussion and systematic results of this review.

REFERENCES

1. Gautam A, Jain S. Assessment of Prevalence of Periodontal Disease and Treatment Needs in the General Population : A Hospital Based Study. Galore Int J Heal Sci Res. 2019;4(June):13–7.
2. Sakti ES. Hasil Utama RISKESDAS. Jakarta Selatan. 2018; 1-8
3. Michael G. N, Takei H, R. Klokkevold P, Carranza F. Newman and Carranza's Clinical Periodontology 13th ed. Clin Periodontol. 2018; 55-69

4. Hughes FJ, Ghuman M, Talal A. Periodontal regeneration: A challenge for the tissue engineer? Proc Inst Mech Eng Part H J Eng Med. 2010;224(12):1345–58.
5. Sulijaya B, Takahashi N, Yamazaki K. Host Modulation Therapy using anti-inflammatory and antioxidant agents in periodontitis: A review to a clinical translation. Arch Oral Biol [Internet]. 2019;105(May):72–80. Available from: https://doi.org/10.1016/j.archoralbio.2019.07.002
6. Mark Bartold P, Van Dyke TE. Host modulation: controlling the inflammation to control the infection. Periodontol 2000. 2017;75(1):317–29.
7. Husson MO, Ley D, Portal C, Gottrand M, Hueso T, Desseyn JL, et al. Modulation of host defence against bacterial and viral infections by Omega-3 polyunsaturated fatty acids. J Infect [Internet]. 2016;73(6):523–35. Available from: http://dx.doi.org/10.1016/j.jinf.2016.10.001
8. Azuma MM, Gomes-Filho JE, Ervolino E, Pipa CB, Cardoso C de BM, Andrada AC, et al. Omega-3 Fatty Acids Reduce Bone Resorption While Promoting Bone Generation in Rat Apical Periodontitis. J Endod. 2017;43(6):970–6.
9. Woelber JP, Bremer K, Vach K, König D, Hellwig E, Ratka-Krüger P, et al. An oral health optimized diet can reduce gingival and periodontal inflammation in humans - a randomized controlled pilot study. BMC Oral Health [Internet]. 2016;17(1):1–8. Available from: http://dx.doi.org/10.1186/s12903-016-0257-1
10. Stańdo M, Piatek P, Namiecinska M, Lewkowicz P, Lewkowicz N. Omega-3 polyunsaturated fatty acids epa and dha as an adjunct to non-surgical treatment of periodontitis: A randomized clinical trial. Nutrients. 2020;12(9):1–14.
11. Nicolai E, Sinibaldi F, Sannino G, Laganà G, Basoli F, Licoccia S, et al. Omega-3 and Omega-6 Fatty Acids Act as Inhibitors of the Matrix Metalloproteinase-2 and Matrix Metalloproteinase-9 Activity. Protein J. 2017;36(4):278–85.
12. Hajishengallis G, Chavakis T, Lambris JD. Current understanding of periodontal disease pathogenesis and targets for host-modulation therapy. Periodontol 2000. 2020;84(1):14–34.
13. Antona ME, Ramos C, Stranges A, Monteiro AF, Gonzales Chaves MM, Mandalunis P, et al. Fish oil diet effects on alveolar bone loss, in hypercholesterolemic rats. Arch Oral Biol [Internet]. 2020;109(September 2019):104553. Available from: https://doi.org/10.1016/j.archoralbio.2019.104553
14. Azuma MM, Cardoso C de BM, da Silva CC, de Oliveira PHC, Jacinto R de C, Andrada AC, et al. The use of Omega-3 fatty acids in the treatment of oral diseases. Oral Dis. 2020;(September):1–11.
15. Ardi L. Manfaat Omega-3 Parenteral di Dunia Medis. Farmasi. 2019;46:12–5.
16. Martinez GL, Koury JC, Brito F, Fischer RG, Gustafsson A, Figueredo CM. The impact of non-surgical periodontal treatment on serum levels of long chain-polyunsaturated fatty acids: A pilot randomized clinical trial. J Periodontal Res. 2014;49(2):268–74.
17. Deore GD, Gurav AN, Patil R, Shete AR, NaikTari RS, Inamdar SP. Omega-3 fatty acids as a host modulator in chronic periodontitis patients: A randomised, double-blind, palcebo-controlled, clinical trial. J Periodontal Implant Sci. 2014;44(1):25–32.
18. Chee B, Park B, Fitzsimmons T, Coates AM, Bartold PM. Omega-3 fatty acids as an adjunct for periodontal therapy—a review. Clin Oral Investig. 2016;20(5):879–94.