International Journal of Dentistry Research

Systematic Review

ISSN: 2581-3218
IJDR 2021; 6(2): 68-71
Received: 11-04-2021
Accepted: 24-06-2021

www.dentistryscience.com
doi: 10.31254/dentistry.2021.6209

Effect of omega 3 fatty acids plus low dose aspirin as a host modulating agent in the treatment of periodontitis patients- A Systematic Review

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Abstract

Background and Objectives: Host Modulatory Therapy is a treatment modality for periodontal diseases. It aims at reducing the periodontal destruction and enhances the regenerative capacity of periodontal tissues. Various host modulating agents are used as an adjunct to scaling and root planing. Omega 3 Fatty acids and non-steroidal anti-inflammatory drugs like Aspirin modify the activity of inflammatory mediators and exert anti-inflammatory effect. The objective of the systematic review was to evaluate the effect of Omega 3 Fatty acids plus low dose Aspirin as adjunct to mechanical debridement in reduction of pocket depth in patients with periodontitis. **Methods:** In this systematic review, Randomized controlled trials in subjects with periodontitis in age group of 25-70 years were considered. Follow up period ranged from 6 weeks to 6 months. A systematic review of literature was performed using Pubmed, PMC, Google scholar, EBSCO host databases. Studies concerning the use of Omega 3 Fatty acids plus low dose Aspirin as host modulating agent in periodontitis treatment were selected. A total 2650 of studies were selected through search strategy and 5 articles which attained the inclusion criteria have been included in present systematic review. **Results:** Oral supplementation of omega 3 fatty acids in combination of low dose Aspirin as adjunct to mechanical debridement reduces the pocket depth during the 6 weeks to 6 months follow up period. **Limitations:** There are limited studies which are available. Also there is lack of data evaluating the long term follow up of the intervention. **Conclusion:** Use of omega 3 fatty acids and low dose aspirin in periodontitis patients improves periodontal status but further long-term studies need to be conducted.

Keywords: Omega 3 fatty acids, Low dose aspirin, Periodontitis, Host modulating therapy.

INTRODUCTION

Periodontitis is immune-inflammatory disease and if untreated it leads to disease progression and finally leading to tooth loss. Host modulating therapy reduces tissue destruction and stabilizes or regenerates periodontal structure [1].

The conventional periodontal treatment which includes mechanical debridement helps to decrease the bacterial overload. Some subjects are unresponsive to such treatment. Current evidences support the beneficial use of host modulating agents as adjuncts in mechanical periodontal therapy [2].

Host Modulating therapy upregulates the protective and regenerative response of host. HMT consist of agents which are given locally or systemically in periodontal therapy and are used as adjuncts to conventional periodontal treatment. The goal of HMT is to control the increased inflammatory processes and enhance wound healing. Different drugs used as host-modulating agents include: NSAIDs, Tetracycline, bisphosphonates and PUFAs [6].

Long chain fatty acids have antiinflammatory action and also have broad range of antibacterial activity by inhibiting periodontal pathogens like P. gingivalis, F.nucleatum, P.intermedia. Omega 3 fatty acids including DHA, EPA are shown to have anti- inflammatory action in rheumatoid arthritis, cystic fibrosis, ulcerative colitis, periodontitis etc. They alter PMN function, modulate lymphocyte proliferation, and enhance endogenous host antioxidant capacity. They reduce synthesis of proinflammatory arachdonic acid metabolites via COX and LOX pathway. Aspirin has anti-inflammatory, analgesic, anti-pyretic and anti - platelet action. Different studies have shown that there is improvement in periodontal health by use of low dose aspirin [6, 7].

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Rationale of present systematic review is that the combination of Omega 3 fatty acids plus aspirin exerts a synergistic effect in reducing inflammation. The low dose aspirin exerts an anti-inflammatory action and omega 3 fatty acids helps in resolving the existing inflammation by releasing the lipid mediators like resolvin and protectin.

The objective of the present systematic review is to compare combination of omega 3 fatty acids and aspirin with placebo in reduction of probing pocket depth in periodontitis patients.

Registration number

The systematic review is according to the PRISMA review protocol (Access-EQUATOR network). The registration number for present systematic review is CRD42020214428

Eligibility criteria, Information source, and Search

In this systematic review, Randomized controlled trials in subjects with periodontitis in age group of 25-70 years were considered with comparison between combination of omega 3 fatty acids and aspirin with placebo in reduction of probing pocket depth. Follow up period ranged from 6 weeks to 6 months. A literature search was performed in PubMed, PMC, Google scholar and EBSCO host databases for papers published from 2010 up to September 2020. Papers published in English language were selected for analysis. Keywords used for study identification in all databases were "(Omega 3 fatty acids AND low dose aspirin) AND periodontitis" and "(Omega 3 fatty acids) AND (low dose aspirin) AND periodontal disease AND Host modulation therapy. The systematic review was elaborated according to PRISMA guidelines.

Study selection

The inclusion and exclusion criteria of the selected studies is given as follows:

Inclusion Criteria:

1. English language articles
2. Randomized controlled clinical trial.
3. Trials with 6 weeks to 6 months follow up
4. Studies involving oral supplementation with combination of Omega 3 fatty acids and low dose aspirin in mild to advanced periodontitis subjects
5. Age group: 25 – 70 years

Exclusion Criteria:

1. Presence of systemic diseases
2. Absence of periodontitis

The selected studies were screened for titles and abstract. The significant studies were obtained in full which were evaluated separately by two investigator and any disagreements were discussed and solved by third author.

Data collection process

The data was collected from all studies and evaluated as following: test group, control group authors, publication year, country, sample size, study design, results.

Risk of bias in individual studies

Cochrane Risk of Bias Tool for Randomized Controlled Trials was used as a tool for assessing bias risk in systematic review

PRISMA 2009- FLOW DIAGRAM

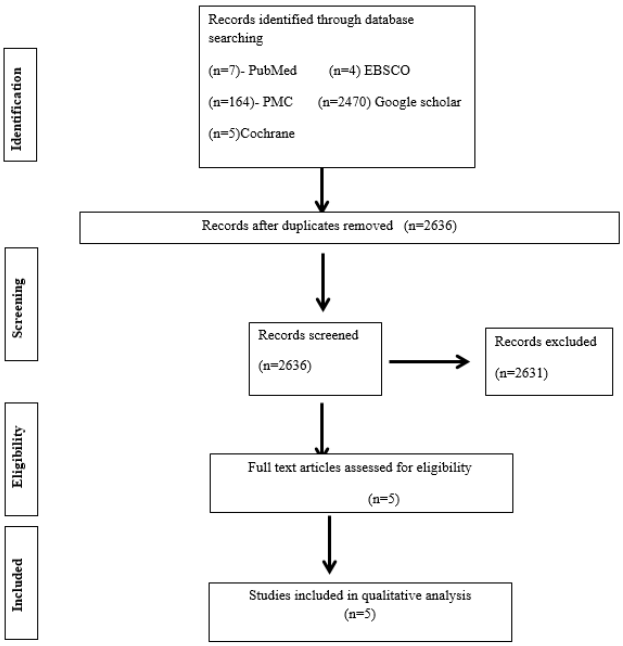


Figure 1: Flow diagram of the literature search and selection criteria (PRISMA)

Table 1: Descriptive characteristics of included studies

SR NO	AUTHOR, YEAR	TITLE	TEST GROUP	CONTROL GROUP	STUDY DESIGN	AGE GROUP	FOLLOW UP	RESULTS
1.	El-Sharkawy H *et al*, 2010 Nov	Adjunctive Treatment of Chronic Periodontitis With Daily Dietary Supplementation With Omega-3 Fatty Acids and Low-Dose Aspirin	SRP followed by dietary supplementation of fish oil (900 mg EPA + DHA) and 81 mg aspirin daily	(SRP) and placebo	Parallel-design, double-masked clinical study	advanced chronic periodontitis- 30 to 70 years of age	6 month	After 3 and 6 months there was statistical significant reduction in probing depths and significant attachment gain
2.	Elkhouli AM, 2011 Apr	The efficacy of host response modulation therapy (omega-3 plus low-dose aspirin) as an adjunctive treatment of chronic periodontitis (Clinical and biochemical study)	decalcified freeze-dried bone allograft (DFDBA) + omega-3 polyunsaturated fatty acids combined with low-dose aspirin	DFDBA + placebo	A randomized, double-blind, placebo-controlled study	moderate to severe chronic periodontitis 35–60 years of age	6 months	There was greater mean probing pocket depth reduction ($P < 0.001$) and gain in clinical attachment ($P < 0.05$) in comparison with the control at 6 month follow up

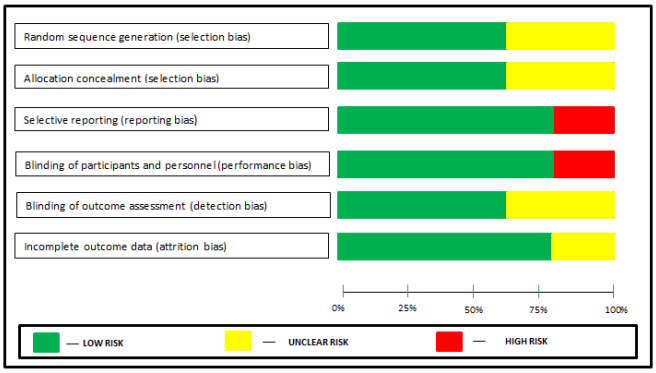
3.	Naqvi AZ *et al*, 2014 Aug	Docosahexaenoic Acid and Periodontitis in Adults: A Randomized Controlled Trial	2,000 mg of DHA capsules + 81 mg of Aspirin	Placebo	double-blind placebo-controlled pharallel trial	moderate periodontitis->40 years	3 months	significant improvement of 2mm in Pocket depth seen in DHA. DHA reduced the number of sites with PD</= 5 mm.
4.	Farhad SZ *et al*, 2014 Oct	Adjunctive Low-Dose Aspirin plus Omega-3 Fatty Acid versus Low-Dose Doxycycline on Chronic Periodontitis	Group 1: 300mg Omega-3 tablet plus 80mg aspirin tablet Group 2: 20mg doxycycline capsule	Placebo	clinical trial	mild to moderate chronic periodontitis-25-45 years	6 weeks	Mean PPD after intervention significntly improved compared to baseline
5.	Naqvi AZ *et al*, 2017 Sep	The Impact of Docosahexaenoic Acid Therapy on Subgingival Plaque Microbiota	2000 mg DHA capsules enriched with 81 mg aspirin	placebo capsules	randomized, double-blind, placebo-controlled trial	moderate-severe periodontitis->40 years	3 months	The combination of DHA +Aspirin had benefit on pocket depth.

Table 2: The mean PPD before and after intervention

STUDY	TEST	CONTROL
El-Sharkawy H *et al*	Baseline: 4.2 ± 0.9 3 months: 2.4 ± 1.1 6 months: 2.2 ± 0.8	4.4 ± 0.7 3.1 ± 0.8 3.0 ± 1.0
Elkhouli AM	Baseline: 5.6 ± 0.8 3 months: 3.7 ± 0.8 6 months: 3.4 ± 0.6	5.8 ± 0.7 4.4 ± 0.7 4.3 ± 0.6
Naqvi AZ *et al*	Baseline: 2.5 ± 0.4 3 months: 1.8 ± 0.4	2.6 ± 0.4 2.06 ± 0.4
Farhad SZ *et al*	Baseline: 3.4 ± 0.7 6weeks: 2.1 ± 0.8	3.5 ± 0.8 2.9 ± 0.8
Naqvi AZ *et al*	Baseline: 2.5 ± 0.3 3 months: 2.5 ± 0.2	2.6 ± 0.4 2.6 ± 0.5

Table 3: Cochrane Risk of bias tool for randomized controlled trial for quality assessment of studies.

	El-Sharkawy H *et al*	**Elkhouli AM**	**Naqvi AZ *et al***	**Farhad SZ *et al***	**Naqvi AZ *et al***
Random Sequence Generation	Low	Low	Unclear	Unclear	Low
Allocation Concealment	Low	Low	unclear	Low	Unclear
Selective Reporting	Low	Low	low	High	Low
Blinding of participants	Low	Low	low	Low	High
Blinding of outcome assessment	Low	Low	low	unclear	unclear
Incomplete Outcome Data	Low	Low	unclear	Low	Low



SYNTHESIS OF RESULTS

El-Sharkawy H *et al* conducted study where control group was treated with SRP and placebo and test group was treated with SRP followed by dietary supplementation of fish oil and 81mg aspirin daily. Saliva samples were obtained for evaluation. After 3 and 6 months a significant reduction in probing depths and a significant attachment gain was observed in omega-3 group.

Elkhouli *et al* included patients with single grade 2 furcation defects. The experimental group received DFDBA+ omega 3 fatty acids combined with low dose aspirin and control group received DFDBA + placebo. At 6 month follow up, the experimental intervention resulted in a greater mean probing pocket depth reduction and gain in clinical attachment level.

Naqvi AZ *et al* included patients with moderate periodontitis and patients received 81 mg aspirin and 2000mg DHA. Gingival crevicular fluid samples were analyzed for changes in high sensitivity C-reactive protein and IL-6 and 1-b. post intervention the mean pocket depth reduced and gingival index values reduced. DHA in combination with aspirin, significantly improved periodontal outcomes in people with periodontitis thus indicating its potential therapeutic efficacy.

Farhad SZ *et al* included chronic periodontitis received phase 1 of periodontal therapy and received one of following daily drug regimen: omega fatty acids plus aspirin, doxycycline, placebo. After 6 weeks mean values bleeding on probing (BOP), Periodontal pocket depth and CAL in both test groups decreased significantly compared to placebo. However the reductions in omega 3 group were significantly greater than those in doxycycline group.

Naqvi AZ *et al* included patients with moderate to severe periodontitis and intervention group received 2000mg DHA enriched with 81 mg Aspirin. After 3 months total bacterial count and individual species count in dental plaque did not differ significantly between baseline and 3 months in either group. There was improvement observed in overall clinical parameters after intervention with DHA and aspirin.

Summary of evidence

From previous studies it has been suggested that dietary supplementation with omega -3 fatty acids and aspirin has improved the clinical parameters in periodontitis patients.

There is high level of evidence proving significant reduction in salivary RANKL, MMP-8, probing depth and significant attachment gain by dietary supplementation of fish oil and 81mg aspirin in periodontitis patients [2].

Also the combination of DFDBA+omega 3 fatty acids+low dose aspirin in periodontitis patients resulted in greater mean probing pocket depth [1].

There is poor level of evidence suggesting reduction in PPD, BOP and CAL gain of omega 3 fatty acids plus aspirin group as compared to doxycycline administration in periodontitis patients [3].

A review by Chee B *et al* stated that inflammatory markers in periodontitis are reduced when fish oil supplements rich in long chain fatty acids are used as adjuncts to non-surgical periodontal debridement. It is also evident that addition of aspirin to Omega 3 fatty acids significantly improved clinical outcomes.

A randomized controlled trial by Rosenstein *et al*, 2013 found a significant decrease in PD and gingival index in patients supplemented with 3000 mg of daily omega 3 fatty acids compared to placebo. A prospective observational study by Iwasaki, 2010 and a cross-sectional nationally representative study by Naqvi *et al*,2010 of fatty acids and periodontitis showed inverse relationship between dietary DHA intake and serum hsCRP.

Also it has been found in various studies that Aspirin and aspirin triggered lipoxins reduce gingival inflammation, pocket depth and attachment loss. Aspirin enhances the endogenous resolution pathways of inflammation.

This systematic review shows that dietary supplementation of omega 3 fatty acids in combination of low dose Aspirin as adjunct to mechanical debridement reduces the pocket depth and gingival inflammation scores during the 6 weeks to 6 months follow up period.

Limitations:

There are limited studies which is available. Also there is lack of data evaluating the long term follow up of the intervention. Also blinding of participants is difficult as the patient has to consume the supplementation orally. There can be selection bias as there is no consideration of multicentred clinical trials.

CONCLUSION

The present systematic review found significant reduction in pocket depth and gingival inflammation scores by the use of omega 3 fatty acids and low dose aspirin thus improve periodontal status in periodontitis patients.

Future considerations

There is need for multicentred clinical trials with fixed dose combination of omega 3 fatty acids and low dose aspirin as host modulating agent.

Conflict of interest

The auther reports no conflicts of interest.

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HOW TO CITE THIS ARTICLE-
Naik P, Benjamin A, Paralkar S. Effect of omega 3 fatty acids plus low dose aspirin as a host modulating agent in the treatment of periodontitis patients- A Systematic Review. Int J Dent Res 2021; 6(2):68-71. doi: 10.31254/dentistry.2021.6209